

A HISTORY OF TROPICAL MEDICINE

The ink of Science is more precious than the blood of the martyrs
Arabian Proverb

Though thou hast made a general survey
Of all the best of men's best knowledges,
And knew so much as ever learning knew,
Yet did it make thee trust thyself the less
And less presume — And yet when being mov'd
In private talk to speak, thou didst bewray
How fully fraught thou wert within, and prov'd
That thou didst know whatever wit could say
Which show'd thou hadst not books, as many have,
For ostentation, but for use, and that
Thy bounteous memory was such as gave
A large revenue of the good it gat
Witness so many volumes, whereto thou
Hast set thy notes under thy learned hand,
And mark'd them with that print, as will show how
The point of thy conceiving thoughts did stand,
That none would think, if all thy life had been
Turn'd into leisure, thou couldst have attain'd
So much of time to have perus'd and seen
So many volumes that so much contain'd

DANIEL — *On the Death of the Earl of Devonshire*

Stand shoulder to shoulder, fighting for the spiritual progress of
humanity, fighting in the cause of the great trinity of the true, the good,
and the beautiful

ERNST HAECKEL

Having now finished what I proposed to offer I most earnestly
and fervently implore the true, the Almighty Physician to shed the influence
of His blessed Spirit on these my labours, most humbly and devoutly
trusting that, should it please Him to make me, thus, an instrument, by
which a ray of light may be thrown on the dark path of Tropical Pathology,
He will be graciously pleased to render that light more vivid, and those
minds it is intended to illumine still more open to receive its impression,
so that a more clear perception of the obstacles, difficulties and dangers
they have to encounter in their road may be established, thereby giving
that road more smoothness, more safety and more simplicity, in conducting
them to the grand object of our united efforts, the preservation of health
and the cure of disease where the former has been uncertain and
the latter too often impossible under existing circumstances

COLIN CHISHOLM

A HISTORY OF TROPICAL MEDICINE

Based on

THE FITZPATRICK LECTURES

Delivered before the Royal College of Physicians of London
1937-38

BY

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IN TWO VOLUMES

VOLUME I

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PREFACE

It is with mingled feelings of pride and diffidence that one receives an invitation to deliver the FitzPatrick Lectures. Pride in that one should have been thought worthy of selection by the President and Censors of the Royal College of Physicians of London to rank with the illustrious men who have had this honour in the past, diffidence—or, as Burke would say, trembling solicitude—arising from consciousness of the difficulty it seems at times an impossibility, of attaining the high level established by one's predecessors. With what joy, what interest, what wonder we read, nearly a quarter of a century ago, Rivers's *Medicine, Magic and Religion*, how we marvelled at the erudition and research displayed by Sir Clifford Allbutt in *Greek Medicine in Rome*, Raymond Crawford's *Pestilence and Plague in Art and Literature*, and there are many others. We long to emulate these monuments of industry, these works which, if nothing else of theirs remained, would suffice to keep green the memories of their authors, and we draw back afraid. In very truth there were giants in those days!

With regard to choice of subject in my case, fortunately, there was no difficulty, the difficulty is in the fulfilment. Here and there scattered in medical works dealing with diseases in the tropics we find a few notes on the history of these diseases but, speaking in any sense other than the narrowest, there is no history of the rise and development of tropical medicine and yet the subject is of absorbing interest. It is a most fascinating occupation to study the early, vague, empirical ideas as to the causation of a disease, to trace the beginnings of rational thought thereanent, the interpenetration of scientific notions and empiricism, the progressive clarification of the haze of doubt to the final solution of the problem.

In the case of so-called Tropical Medicine the difficulty has been the greater because it has necessitated tracing back, in some instances, to times of savagery, the earliest available records, and to legends prior to record. In others the first traces had to

be sought in articles, in books, in references in foreign languages, works attainable with much difficulty and often only in garbled or mutilated copies the originals of which had been lost

Another difficulty, and a very real one, consists in the fact that we have no definition of the term 'Tropical Medicine'. If we take its narrow interpretation as 'disease restricted to the tropics,' i.e. to $23^{\circ} 27'$ of latitude on either side of the equator, we could with a close approximation to the truth say that it is non-existent. If we extend our limits to 'diseases met with in warm climates,' this apparently small extension in reality comes to include nearly all the ills that flesh is heir to, except, perhaps, frost-bite, and even that might occur on the mountain heights of a country generally regarded as among warm climates—Fujiyama, Kilima-Njaro, Mount Kenya, for example.

Yet again, we encounter further difficulties if we cut the Gordian knot by deciding to study the *prevailing* diseases in warm climates, for we find curious changes in distribution when we try to trace their histories. Thus, there are several diseases which, though now they are almost confined to torrid zones, in former times were found in temperate climates also, among these we may mention malaria, cholera, plague, relapsing fever, leprosy, ankylostomiasis and other helminthic infestations, and, as regards British possessions at least, smallpox and typhoid fever.

A second group would consist of diseases which have never become widespread beyond warm countries, though purely as a fortunate chance because the vectors had not been introduced from their original habitat, or, if they had, they had not succeeded in flourishing. As members of such a group we may enumerate yellow fever, human trypanosomiasis, leishmaniasis, melioidosis, clonorchiasis, paragonimiasis, onchocerciasis, filariasis, certain tick-borne infections, Japanese River fever, Rocky Mountain fever, some varieties of endemic typhus.

A third group there is, comprising diseases which are often considered as tropical, but are in reality widespread, such, for example, as undulant fever, long regarded as limited to Malta and the Mediterranean, but now known, from inclusion of *abortus* fever, to be almost universally distributed. Another member of this group is amœbic dysentery which caused a serious epidemic in Chicago in 1935, also sprue, pellagra, alastrim, tularæmia and, again, varieties of typhus.

Before we can make any true progress in the study which we have set ourselves we must decide upon the starting-point. When

we come to consider this question we find, fortunately, that the problem to a great extent carries its own solution. It is not our aim to give a history of diseases of warm climates, but a history of tropical medicine in the generally accepted connotation of the term. The former—history of diseases in warm climates—would necessitate going over ground already well covered, discussion of malaria, plague, and perhaps other diseases from the dawn of history, but the latter—the subject of these lectures—is the history, that is, the rise and development of tropical medicine. Its starting-point can only be that time when reason began to throw its light upon and illumine the darkness of empiricism, when people began to theorize regarding causation of disease, to consider the problems scientifically, and that rarely takes us back more than a hundred to a hundred and fifty years.

In the following pages the reader will often find reference to times long antecedent to this, the reason is that some of the more modern ideas on ætiology, pathogeny and treatment originated in ancient empiricism and their history would be incomplete if such were disregarded.

Let us, therefore, state in a few words the plan it is proposed to follow. As a preliminary we will attempt to describe from the medical aspect the state of some of the countries when they first came under European rule. This will show us the nature of the problems that arose and the conditions under which their solutions had to be undertaken. We can then trace how improvements have been brought about, usually first with a view to safeguarding the health of officials and European traders, and later undertaking also the treatment of natives by which two purposes would be simultaneously accomplished—benefit to the health and well-being of the native and further protection of the white man from native-born infection. Local preventive measures would soon have to be expanded to include public health on a wider scale, conservancy, water-supply, refuse-disposal and, in colonies with a littoral, port sanitation, quarantine, and prevention of introduction from or export to other countries of infection by air traffic. Later still, philanthropy would make an ever-increasing claim on the governing race. Then the welfare of the native comes to take first place—hygienic education of the native, housing, feeding, safeguarding of mothers, matters of child welfare and so on to training of the natives as orderlies, nurses, midwives, dispensers, sanitary inspectors, and subordinate medical officers.

We shall have to consider also the state of the Navy and of the Mercantile Marine as it was a century or more ago, for medical

officers in the senior service were well to the fore in investigating the diseases of warm climates. The names of James Lind, Sir Gilbert Blane, Thomas Trotter, Sir William Burnett, spring at once to our minds. We must not forget the laymen who did much for the health of seamen. To give due meed of praise to Captain Cook for preserving his crews from scurvy will in no way detract honour from the work of Lind. Improvements in quarters, accommodation, food, all have played a large part in ameliorating the health of the seaman. In an analogous way army medical officers saw much of tropical disease in expeditions abroad, in India and in the Colonies, and some of them wrote most painstaking works on barracks, on food, on the care of the soldiers' health, apart from learned disquisitions on the diseases they encountered. Names to be held in honour among these are Sir John Pringle, Robert Jackson, Sir Ranald Martin, Desgenettes.

The history and elucidation of the causation and the stages in the evolution of ideas, first of empirical and through them of rational methods of treatment, form a fascinating study. The generation preceding our own, the medical men of the latter part of the nineteenth century, used to speak with no little contempt of the ignorance and superstitions of the generation before them. We in our day find it hard to regard seriously many of the views held seventy to eighty years ago on the causation of disease and our successors will almost certainly be equally scathing in their remarks of what we consider correct in these enlightened days. We are surprised to read in Bascome's works in 1851 in *A History of Epidemic Pestilences from the Earliest Ages with Researches into their Nature, Causes and Prophylaxis*

The supposition of the existence of any new disease in our day is untenable, but to be accounted for because of our inability to trace diseases under the same names and precise characteristic symptoms described by our predecessors in the study of nature, in fact the comparatively modern origin of some diseases may be said to rest on the absence or deficiency of distinct and express notice of them in the writings of the ancients, arising in some measure from false or imperfect translations from the original, and from the practice of the ancients in referring different malignant maladies to the same pestilential constitution.

Again, Dr Knapp in the *New York Medical Journal* of 1878 notes the influence of astrology on ideas of disease.

The approach of one or more of the great planets of the solar system occasioned disturbance in the atmosphere, causing great heat and cold,

raints, drought, blighting of crops and fruits, and epidemic diseases among the human race, and epizootics among animals

In 1864 electric tension was thought to play a large part in promulgation of epidemic and other diseases. Thus, in a work *On the Influence of Variations of Electric Tension as the Remote Cause of Epidemics and Other Diseases* William Craig of Ayr contended that all the usually regarded influences of filth, impure air, contagion, miasmata, are as nought in the production of epidemics compared with variations in electric tension. That disease arose from putrefying animal and vegetable matter was common belief in and since Roman times, and Shakespeare makes Henry V before the battle of Agincourt say

“ A many of our bodies shall no doubt
Find native graves, upon the which I trust
Shall witness live in brass of this day's work,
And those that leave their valiant bones in France,
Dying like men, though buried in your dung-hills,
They shall be fam'd, for there the sun shall greet them,
And draw their humours reeking up to heaven,
Leaving their earthly parts to choke your chime—
The smell whereof shall breed a plague in France ”

Astonishing, in fact almost inconceivable, was the state of insanitation, even as late as the latter part of the eighteenth century. Bascome writes

Until this time [1760] extraordinary as it may appear, there was not any such thing as a privy in Madrid, it was customary to throw ordure out of the windows at night, and it was removed by scavengers the next day. An ordinance having been issued by the King that every householder should build a privy, the people violently *opposed* it as an arbitrary proceeding, and the *physicians* remonstrated against it, alleging that the filth absorbed the unwholesome particles of the air, which otherwise would be taken into the human body! His Majesty, however, persisted, but many of the citizens, in order to *keep their food wholesome*, erected their privies close to the kitchen fire-places

Houses in England in the time of Henry VIII were far from ideal. In Epistola 13, Lib. xxii, of Erasmus, we read

Conclavia solâ fere strata sunt argillâ, tum scirpis palustribus, qui subinde sic renovantur ut fundamentum maneat aliquoties annos viginti sub se fovens sputa, vomitus, inictum caninum et hominum, projectam cerevisiam et piscium reliquias, aliasque sordes non nominandas

(The rooms are usually floored merely with clay and rushes which are renewed in such a way that the lowest layer remains, it may be for some twenty years, incubating spit, vomit, the urine of dogs and men, beer dregs, fish remains and other indescribable filth)

He adds that Holland had been freed from the sweating sickness by changes made in the houses

To return from this digression In the course of this study we shall take occasion to note the reciprocal effects of history and large movements and engineering undertakings on the one hand and tropical disease on the other, the medical aspects of the difficulties of construction of the Suez Canal and the Panama Canal and how they were overcome, the effects of the African slave-trade in spreading disease and the conditions under which the trade was carried on The evils as well as the advantages of irrigation, of opening up a country by the building of railways, construction of roads, and of contact between countries by means of an air-service, these will be mentioned incidentally only, as the question is bound up with non-medical matters, and to attempt to discuss them in any detail would take us too far afield

Discovery of the cause of a disease constitutes an enormous advance towards its elimination As long as causes are still unknown it is but a truism to say that treatment is empirical and prevention scientifically difficult Knowledge of the cause sometimes enables us to cure a disease and more often enables us to prevent its results But that much can be done, particularly in the direction of prevention of disease, although we are as yet ignorant of its cause, is exemplified in the case of yellow fever Havana, Panama, many parts of South America were freed from this scourge through application of epidemiological knowledge in spite of our ignorance of the actual cause

Before their causes were determined, little more than half a century ago, again and again does history show us how "civilizations have retreated from the plasmodium of malaria, armies have crumbled under the onslaught of the cholera spirillum or of dysentery and typhoid bacilli Huge areas have been devastated by the trypanosome" (Zinsser)

Many pitfalls lie in the path of inquiry into diseases of old time, they were first described by militant commanders, non-medical explorers, often under local names, and it is sometimes difficult to correlate their descriptions with any morbid condition known in our day Again, diseases are not static but have undergone changes which may be so great as to make them no longer recognizable to-day Even in our time we have seen how scarlet fever has altered from the dreaded fatal disease of fifty years ago, enteric fever is comparatively mild in Britain in contrast with its characters in the tropics, smallpox is hardly even a menace now-

adays, on account of its change from severity to mildness—some people, even civilized people, dread it less than protective vaccination

Many are the instances which might be quoted as to the effects of disease on history and what a monumental work a discussion of such would be. This aspect is not within our scope, but transitory mention may be of interest. From the Greek historian we read how the plague of Athens kept the Athenians from attempting to drive off the Lacedæmonians from Attica, how the Peloponnesians hurried from Attica owing to fear of it, how the disease accompanied the Athenian fleet and interfered with its attack on the Peloponnesian coast. Again, Xerxes's invasion of Greece was brought to nought and the expedition abandoned after the loss of nearly half his force from plague and dysentery. In 390 B C plague put a stop to Hannibal's advance to settle in Sicily, Marius owed his victory over Octavius in 88 B C to the epidemic which, historians tell, destroyed 17,000 of the army of the latter. Five hundred years later a devastating epidemic led the Huns to abandon their advance on Constantinople. The Crusades afford several instances that under Baldwin never even reached Jerusalem owing to devastation of his army by bubonic plague, that of 1250 was ruined by scurvy and that of 1270 by dysentery. Charles I in 1643 might have marched from Oxford to London and thus have changed the whole aspect of the Civil War had he not been stopped by typhus among the troops, in 1708 the Swedes, though winning in Southern Russia, had to withdraw because of plague. The French Revolution might have had a very different history had the Prussians under Frederick William II not had to retreat after losing more than a third of their complement from dysentery. The Haitian Republic (as we have told elsewhere) owes its very existence to yellow fever, only 7000 surviving out of 30,000 of Napoleon's picked troops. Other instances might be given, but these will suffice.

There is another aspect which is of more importance to those interested in tropical medicine and which deserves to be mentioned, and that is the evil results which may unfortunately ensue on the best of intentions

The best-laid schemes o' mice an' men
Gang aft agley

Some of these will come under consideration in the course of

this work Here we must rest content with little more than the bare enumeration of a few of them Professor Leiper has shown how irrigation in the Asswan Province, undertaken at great cost and with the best intentions, led to the spread of schistosomiasis At Komombo is a plain of some 100,000 acres about 40 feet above high Nile level In this dry and barren area there was no schistosomiasis A small strip close by was cultivated by basin irrigation and resulted in the production of one crop annually Some of the people in this small strip suffered from schistosome infestation, but on account of the periodic drying of the soil the disease did not spread to any great degree In 1904 certain capitalists were attracted by the potentialities of the vast plain, they cut canals, introduced pumping apparatus and recruited 30,000 or so labourers to keep an area of between 20,000 and 30,000 acres under continual cultivation, with the result that larger crops were raised and two yearly in place of one In 1926 examination revealed a 75 per cent infestation of the labourers and abundance of the molluscan host, *Bulinus*, in the irrigation canals, perhaps pumped in from the river or multiplying behind the dam

J Allen Scott stated as recently as 1937

With regard to the future extension of areas of high *S. hæmatobium* indexes, we have a more sound basis for prediction It seems all but certain that the conversion of land from the ancient system of basin irrigation to the modern perennial system has caused a marked increase in the prevalence of this species At the present time the government programme calls for similar conversion of approximately 700,000 acres in the next decade The conclusion seems almost inescapable that the proposed changes will not only doom an additional million people to infestation with schistosomiasis, but that the average case in these districts will be at least twice as severe as at present and deaths will probably double Does the economic improvement expected in these areas to be converted warrant the impairment of the health of such a large proportion of the population?

The question of irrigation and its relation to malaria differs from that of schistosomiasis In the case of the latter the whole life of the intermediate host is passed in water, whereas only the egg, larva and pupa stages of the insect host of malaria need water and the danger of irrigation lies in its providing additional sites for the *Anopheles* to breed, i.e. the smaller channels overgrown with weeds, seepage from larger ditches, terminal cul-de-sacs, swamped fields

Again, bonification of land, of which so much has been written in prevention of malaria, especially by the Italians, is not regarded by them as, in the main, an anti-mosquito measure Where boni-

fication is carried to its logical conclusion, agriculture improves, the inhabitants live in better houses, the whole standard of life is raised and malaria becomes less and less important as a cause of sickness

Examples are numerous of increased prevalence of malaria consequent on inundation of rice-fields, installation of irrigation ditches was followed by increase of malaria in British Guiana. The question of irrigation and malaria is a very complicated one. It may reduce malaria, as Bentley has shown in parts of India, by converting many small collections, favourable to mosquitoes, into large ones, mosquito-breeding being rather proportional to length of water edge than to area of water surface. Also a plan suitable for one country, with certain plasmodium transmitters, might be useless in another. For example, open concrete ditches, though quite safe in Palestine, would in Sumatra merely afford opportunities for *A. maculatus* to breed, a method employed with success in Jerusalem would prove useless in Bombay. Such instances might be multiplied. The moral is obvious: no irrigation scheme ought to be put into execution in any malarious or potentially malarious country without a careful preliminary survey, and when it has been taken in hand it should be under the constant guidance of a trained, experienced malariologist.

It is a fact now well known to all malariologists that removal of bush, nominally to get rid of mosquitoes, may be effectual in clearing out some harmless species while opening up the way for incursion of a noxious malaria vector. Extensive deforestation undertaken with a view to facilitating agriculture may so influence rainfall that crops become poor and almost valueless. Pringle, speaking of India, says of one area, "The making of a high level canal has transformed the district into a pest-house."

The Army Sanitary Commission of 1871 noted that fever was more prevalent and more fatal in that part of the country which had canal irrigation than in the unirrigated, unless the latter was naturally a very moist country. It is almost a truism to say that excessive or injudiciously applied irrigation is detrimental to health. In Northern Italy irrigated rice-fields are not permitted within a thousand yards of small towns, and in India wherever irrigation is excessive, so that water stagnates in the subsoil, the prevalence of ague, fevers, and the proportion of persons with enlarged spleens is marked, and in irrigated districts not under constant supervision fever is more common than it was before the installation of irrigation.

We cannot here discuss at length other good or ill effects of

irrigation, but the above are not the only ones. The conversion of many thousands of acres of barren, dry land into a soil perpetually moist and covered by vegetation, the opposite of the deforestation mentioned above, is very likely to have effect on *climate*. In the former case atmospheric humidity is increased with possible effects on rainfall, in Egypt and the Sudan, for example, the former characteristic 'dry heat' has become, in parts at least, the tropical 'moist heat'. The effects on crops is perhaps more of economic than of medical import.

We see, therefore, that the subject of the evolution of tropical medicine and the struggle against disease in the Tropics is an exceedingly complex one with many ramifications, like a tree whose roots lie deep in the dark, but those branches are extensive, fruitful and ever-growing, whose nurture is beyond the capability of one man alone to maintain—in very truth a tree of knowledge to whose cultivation every conscientious worker can add his quota and of whose fruit all can partake and each find something to make him wise.

In ending these prefatory remarks the author is desirous of expressing his thanks to the following: to Lady Leishman for the photograph of Sir William Leishman, to Sir Wilson Jameson, Dean of the London School of Hygiene and Tropical Medicine, to the Honorary Secretaries of the Royal Society of Tropical Medicine and Hygiene, to Dr P H Manson-Bahr, C M G, D S O, and to Professor Patton, for the loan of blocks or photographs, to Dr W A Sawyer and Dr F L Soper of the Rockefeller Foundation for permission to reproduce charts from their papers, and to the Secretary of the League of Nations for a like privilege. The author is much indebted also to Captain R L Sheppard, Secretary to the Bureau of Hygiene and Tropical Diseases, and to the members of the staff of the library of the London School of Hygiene and Tropical Medicine, for their kind and ungrudging help in the irksome task of tracking down references.

Finally, and especially, he wishes to express his thanks to Messrs Edward Arnold & Co for their unvarying courtesy at all times, and for their courage in venturing to undertake the publication of a work whose success is problematical, which can at best bring but small and totally inadequate pecuniary recompense—a work, in short, the fate of which *Θεῶν ἐν γούνασι κεῖται*.

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VOLUME I

INTRODUCTION

The present century, to which we must add the last years of the nineteenth, will be known in the annals of medicine by the immense progress which the science has made in elucidating the ætiology and deducing therefrom measures of prevention of tropical diseases

We must not forget that of diseases now called 'tropical' some at least were in times past rampant in temperate climates, leprosy, cholera, plague are instances. It is important also for us to bear in mind, when we begin to congratulate ourselves on the discovery of their causes, that without any specific being found against plague, against leprosy, against the sweating sickness, they are now practically unknown among us in England. They disappeared, but not because they were driven out by marvellous discoveries in medicine, they faded away before the general amelioration of our state of living as a result of improvements in sanitation—improvements in housing, drainage, refuse disposal, in education and elevation of the standard of living for the generality of the people. Leprosy, malaria, plague were lessening before the *causa causans* had become known

Again, let us not be unduly elated by half-successes. In malaria, with the discovery of the parasite, its mode of development and its transmission, we thought we had gone far, when it was found that one genus only of mosquitoes, *Anopheles*, would transmit infection, we congratulated ourselves that now we had the key to eradication of malaria. We were wrong, that was only a half-way step. We have known it now for nearly forty years, yet malaria in warm climates is as bad, as rife, as prevalent as ever, and nearly as fatal as it was a quarter of a century ago.

It was Sir Malcolm Watson, *primus inter pares*, who laid such stress on the need to go deeper than merely finding the mode of transmission, the vector and the conditions under which it lives so that it can be fought with, he maintains that we must go further back and raise the living conditions of the natives, if that is done, as in England so abroad, we may have better hope and expectation that 'tropical diseases' so-called may disappear there

as they have done in temperate climates We do not mean that these desirable ends are not likely to be reached more quickly and with less waste of effort when we know their causes and the vulnerable points in the life-histories of the vectors and the chain of infection, but that general improvement and the application of our knowledge must not be neglected for research which often is academic in character at first, it must not be allowed to remain so restricted There is a reciprocal action between research and its application, clearly shown in the case of entomology Little was known of entomology until it became associated with the pathological action of insects, then medical research stimulated entomology and entomology stimulated medical research What applies to entomology is equally true of helminthology, protozoology and, in part, to bacteriology

A century, nay, even half a century ago, life in the tropics was regarded as hazardous in the extreme We most of us remember the opinion expressed on the tropics by Sydney Smith, with its characteristic exaggeration based on truth

Insects are the curse of tropical climates The *bête rouge* [an acarine] lays the foundation of a tremendous ulcer In a moment you are covered with ticks Chigoes bury themselves in your flesh and hatch a large colony of young chigoes in a few hours They will not live together, but every chigoe sets up a separate ulcer and has its own private portion of pus Flies get entry into your mouth, into your eyes, into your nose, you eat flies, drink flies and breathe flies Lizards, cockroaches and snakes get into the bed, ants eat up the books, scorpions sting you in the feet Everything bites, stings or bruises, every second of your existence you are wounded by some piece of animal life

An insect with eleven legs is swimming in your teacup, a non-descript with nine wings is struggling in the small-beer, or a caterpillar with several dozen eyes in his belly is hastening over the bread and butter! All nature is alive and seems to be gathering all her entomological hosts to eat you up as you are standing, out of your coat, waistcoat and breeches Such are the tropics All this reconciles us to our dews, fogs, vapours and drizzle—to our apothecaries rushing about with gargles and tinctures—to our old British constitutional coughs, sore throats and swelled faces

Though this is, of course, gross exaggeration, conditions in the earlier years of the nineteenth century were bad and the outlook serious and menacing for those proceeding to the tropics Going in search of a living many succeeded in finding death Seventy years or so ago mortality from yellow fever in the West Indies reached 69 per cent among our garrisons, plague was once the

pestilence of Europe as well as rife abroad, cholera likewise swept over Europe and invaded many of the warmer countries, small-pox was deadly and very common, so common that it was regarded as the right thing to be inoculated with it and have it over

When we come to discuss the chief diseases of warm climates *seriatim* and their histories we shall consider in greater detail the early ideas on them and the dawn of scientific study of their causation. Here we may mention one or two of the more general notions prevalent, they present a curious mingling of acute observation and vague surmise, often approximating to the truth and nearly forestalling discoveries actually not made till perhaps a century later. In many, we might say in most, minds the ideas were of the vaguest. One author of the time writes

It is not so much from the high temperature that we Europeans suffer as the excessive humidity conjoined with it for so many months of the year and both which, commingled with the terrestrial exhalations, tend gradually, through their united influence, by inducing what may be termed a *Cachexia loci*, to undermine the best and most robust of constitutions

Colin Chisholm in his *Manual of Climate and Diseases of Tropical Countries* makes some quaint, some curious, some very shrewd and accurate observations for avoiding the dangers of a tropical climate, bleeding, as might be expected, takes a high place. He noted, as his predecessors had done for centuries, that the miasmata of swamps gave rise to the worst of the endemic fevers, but he worked out from figures he had gathered that mortality from climate alone was not above 1 in 37. By some intricate, at least not obvious, method of calculation he came to the startling conclusion that, allowing for 'pestilence and endemic causes of disease,' the chances are 2 to 1 that an artillery officer will live in the West Indies for four years, taking endemic causes alone he has a 3 to 1 chance. He recommends that on reaching latitude 23° N (i.e. the northern tropics) every newcomer should be bled to an amount proportioned to his age and strength. Anyone who takes the trouble to read his book and see how drastic were his blood-lettings in cases of disease, may make his own estimate of what 'proportioned to his age and strength' might imply. The newcomer is also advised to take 5 grains of calomel at night and saline in the morning frequently and be bled again before landing.

During the voyage to the tropics commanding officers should see that their ships are sweetened by scrubbing and inspersion [a good word, but its meaning is obscure, it does not appear in the dictionaries], fumigating and ventilating. Hammocks are to be

preferred to berths [perhaps because the latter tended to harbour vermin], blankets should be brought on deck during the day for airing, beds or mattresses are not recommended, in fact should be forbidden [may this be because of lice and bugs?], he is in favour of enforcing such exercise as the situation admits and especially dancing. He is in agreement with Sir Andrew Halliday that there should be what he calls 'seasoning barracks' away from marshes and in these new troops should be housed for three or four months on first arrival.

Neglect in keeping the environs of barracks clear of brushwood, long grass and rank weeds leads to remittent fevers and dysenteries. So far good, but his explanation is, to say the least, fanciful.

Giving the human frame the means of accommodating itself to the change of climate seems the most likely to bring the endemic yellow remittent fevers of the west to a level with those of the east, by lessening inflammatory reaction and moderating the orgasm in the hepatic system.

In spite of his dread of marsh exhalations on account of the high mortality among those living near them or stationed near, even temporarily, Chisholm regards the mosquito as a harmless insect if left to bite undisturbed. Speaking of marshes he writes that over a twelfth of the inhabitants of marshy districts annually perish. In 1795 the *Majestic*, Admiral Sir John Laforey's ship, lost in seven weeks 189 men, in 1796, Admiral Harvey's ship, the *Prince of Wales*, lost 97 men "without any suspicion of infection. During 1797 the same ship in the same month of the year lay in the open bay, about a mile from the shore and did not loose [*sic*] a man." Of the insect he says

The insinuation of the sucker of the mosquettoe, another very troublesome insect, is attended with no unpleasant consequence if the person stung abstains from disturbing the insect in its operation, or from rubbing the part after it—a self-denial, however, almost impossible. Obstinate ulcers have been the consequence of breaking off the sucker of the mosquetto by rubbing the part whilst it is employed in sucking.

Chisholm is a little too dogmatic in his subdivision of diseases in tropical climates according to season. His remarks refer mainly to the West Indies but, he says, they apply to all tropical countries. He generalizes thus. The endemic diseases are bilious and inflammatory as the seasons are hot and wet or cold and dry. In the rainy, hot season remittent fevers, dysenteries, colics, cholera morbus, ulcers of the legs and, in marshy districts, obstinate intermittents depending on glandular obstruction or visceral inflammation, yellow remittents of the most concentrated kind and

hepatic dysenteries are very common, frequently epidemic and very fatal "During winter and spring pleurisies with fever, catarrhal fevers, rheumatic fevers, ophthalmias, inflammatory anginas, erysipelas, guinea worm Hepatic inflammation occurs at all seasons, especially in marshy districts" Between the wet and the dry seasons pleurisy and hepatitis, he says, assume a diathesis which has been designated in Europe typhoid, which gives them a character of peculiar danger and insidiousness It is difficult to see what Chisholm was thinking of here

Other diseases he mentions as being unaffected by season, such are yaws, putrid and ulcerous sore throat [but inflammatory anginas he puts among the winter and spring diseases], chronic aphthæ, lepra, tetanus and trismus nascentium, hydrocephalus and hydrophobia Smallpox he places in the same category, this is sometimes confluent and malignant, but, he affirms, "in every instance this disease has been introduced from the coast of Africa by slave ships" His experience with Arachnida cannot have been extensive, for he states that scorpions, scolopendra [centipedes], spiders or Tarantula cause painful inflammation but are 'never poisonous'

Of adventitious sporadic diseases the most important and the least understood was, in his opinion, "malignant pestilential fever," which was "vulgarly, but most improperly, called yellow fever" (see p 314)

Finally, he showed acute powers of observation when he stated that plague infection rarely remains inactive or latent beyond ten days [the incubation period is now regarded as from two to eight days], but "the clothes and other packed baggage of passengers who, after a voyage from places infected, enter sound into the lazarette, are more to be dreaded than their persons"

At that time, and for some years afterwards, scientific ideas on medical questions were slow to develop We can hardly believe that the following was written only seventy-four years ago (in 1864) "The climate of India tends powerfully to the production of disease within the abdominal cavity, while that of Europe tends as powerfully to production of disease within the thoracic cavity" So far, perhaps, we may agree, but behold the reason which is given in these words

As the two hemispheres are divided, the eastern from the western, by the meridional line, so the diaphragm separates the two great cavities of the body, in one of which, the thoracic, is manifested very generally the morbid results of the Western, while in the other, the abdominal, are generally manifested the morbid results of Eastern climates

In the days of Clive it was commonly said that the Englishman returned from the East with a tawny complexion, a bad liver and a worse heart !

Facts were stated—the outcome of years of observation—but expression of opinion as to the causal significance of these facts was wisely withheld. Subsequent research has made many of these clear. The comparatively low mortality among natives—West Indian, Javanese, Parsees, and others—from certain diseases very fatal to the European or to new arrivals generally was again and again observed.

It would seem that such persons [the natives] are exempted, in a great measure, from the influence of morbid causes which destroy prematurely Europeans and other foreigners. That the rate of mortality should be lower among them than in the southern parts of Europe is a fact which, in the present state of our knowledge, is difficult to explain.

Much of this, we know now, was due to immunity resulting from exposure to infection in childhood, *e g* yellow fever and malaria, the contrary is seen when tuberculosis, with which most Europeans in towns are inoculated from their earliest days, enters among a non-immune community, as *e g* the Fijians and the Senegalese. It would be waste of time to dwell on this question which was formerly very puzzling but is now so obvious.

There are so many problems and we often try to dig too deeply at first. When we look back upon some of the discoveries in science, and tropical medicine is but a branch of medical science, how simple they appear, it seems incredible that with the solution of the problem as it were under their very noses, nay, even directly before their eyes, people groped blindly for so many years, even centuries. They were not unobservant people either, they looked with too distant a vision and missed the things that were near.

At the same time let us remember that Nature is no fool. She has not had all these millions of years of experience and experiment without finding out that if thwarted in one way she can attain her ends in another. We thought that the eradication of yellow fever was simple when the vector was known together with the mode of conveyance of infection, and Gorgas acting upon that knowledge cleared up Havana and others effected the same in parts of Brazil and elsewhere. Then suddenly we find yellow fever where there is no *Aëdes*, no apparent initial case, no overcrowding in a seaport town, but cases are encountered in rural, in jungle districts, and the question is all in the melting-pot again and we have to start research anew.

Again, in default of their usual hosts diseases can adapt themselves to others, some harbour the infection but suffer no ill-effects, nevertheless, given the right or any serviceable intermediary and the infection may be transmitted from the healthy reservoir host to susceptible man or other animal

The field to be tilled is wide, the harvest to be gathered is vast and the labourers all too few, but fortunately they are conscientious toilers whose work is thorough and, though the gleaners who follow may find little to reward them in going over the same ground, there are still large tracts which lie waiting to be explored

In the following pages I have dealt with a few of the problems of tropical medicine which confronted our predecessors and have tried to trace their solutions in an orderly manner which, after all, is what we understand by evolution. How inadequately my task has been accomplished I am indeed only too conscious. Volumes might be devoted to telling of the discoveries even in the past sixty years on the subject of insect vectors of disease alone, such as Filariasis by *Culex* (Manson), yellow fever by *Aedes* (*Culex*, Finlay), malaria by *Anopheles* (Ross, Grassi), human trypanosomiasis by *Glossina* (Bruce), African relapsing fever by *Ornithodoros* (Dutton, Todd), Indian relapsing fever by the louse (Carter), plague by *X cheopis* (Ogata, Indian Plague Commission), Rocky Mountain fever by *Dermacentor* (King, McCall), endemic typhus by lice and by ticks (*Rhipicephalus*), Japanese River fever by mites, *Trombidium* (Kitasato), dengue by *Aedes* (Graham, Cleland) and Pappataci fever by *Phlebotomus* (Doerr)

Tropical sanitation in detail, as a separate subject, I have left severely alone, after all it is largely the local application of general measures. Growth and extension of tropical towns have entailed drainage of soil and swamp, piped water-supplies have meant closing of old wells and abolition of cisterns, with consequent reduction of malaria, yellow fever, typhoid and cholera. Maternity and child-welfare schemes have reduced maternal and infant mortality and prevented much permanent invalidism.

We are sometimes tempted to look with ridicule on the quaint views of years gone by, but let us remember—a sort of *memento mori*—that future generations will ridicule some of our dearest tenets of to-day, and that nothing is more easy or more foolish than to censure one age for not possessing the mental equipment of the next.

Yet another point which in the clamour for priority is sometimes forgotten. Science is truly international and knows no

boundaries of nations, languages or creeds (as the Rockefeller Foundation recognized when it was incorporated twenty-five years ago) The advance of knowledge in the causation and prevention of disease is not for the benefit of any one country, but for all—for the lonely African, deserted by his tribe, dying in the jungle of sleeping sickness, or the coolie afflicted with the miseries of beriberi, just as much as for our own citizens

Looking back on the lives of those who have devoted themselves to the study of tropical medicine we find a few have reaped honours for the work they have done, but many there are who toil unrecognized—"Others there be that have no memorial" Such men labour, surrounded by squalor and disease, separated from home comforts, from encouragement, human sympathy and companionship, preserving in silence their lofty ideals, shrinking from publicity, their daily prayer, "Lord, give us work and strength to do the work" But, at their death, unhonoured and unsung, they gain, may we hope, all the honour, the reverence paid to the Unknown Warrior, and in the knowledge of duty done the joys and recompense such as the world cannot give

*Dum brevis hora sinit, discas instare labori,
Venturo nequeas credere Carpe diem!*

To work then now! 'Ere Time's last hour may strike,
To-morrow's too untrusty Snatch to-day!

The second great Fire of London, that of September, 1940, destroyed in its path some two million books, among them nearly 500 copies of this work A re-issue has therefore become necessary, and as certain advances of importance in the History of Tropical Medicine have taken place since the first issue, though not enough to warrant the publication of a new edition, even had the labour and the paper been available, Messrs Edward Arnold and Co have very kindly suggested that an Appendix might serve to embody the chief of these advances, and the author wishes to record his gratitude for such an opportunity

Mere incidental notes, additions and amplifications, which would fittingly find place in a new edition, are not included, but only accounts of larger developments in the realm of tropical medicine, research and discoveries in which are ever presenting matters for discussion and must be included if such a work as this is to be kept up to date

CHAPTER I

THE NAVY AND MERCANTILE MARINE

*Ille robur et æs triplex
Circa pectus erat, qui fragilem trunci
Commisit pelago ratem
Primus*

This was written of the bravery of those who voluntarily faced the dangers of an angry sea in the frail vessels of ancient days. Not a whit less arduous was the lot, even a brief century and a half ago, of the sailor who, sometimes voluntarily, more often not, lived for months on end in close, ill-ventilated quarters, exposed to danger from the elements, to infection from his ship-mates, to sickness, accident, bad food, worse water, and the prospect of discharge only as an invalid to beg his way till death relieved him.

In this chapter we will try to outline the progress of hygiene at sea from the early days when commerce was all and the lot of the sailor quite a secondary consideration. Here is a sketch of the ships of the times of Marco Polo as given by Colonel Yule in his book on the travels of that worthy. To the Persian Gulf came inhabitants of India in ships loaded with spicery and precious stones, pearls, cloth of silk and gold, elephants' teeth and many other wares.

Their ships are wretched affairs and many of them get lost, for they have no iron fastenings and are only statched together with twine made from the husk of the Indian nut. They beat this husk until it becomes like horse hair and from it they spin twine and with this they stitch the planks of the ships together. It keeps well and is not corroded by the sea water, but it will not stand well in a storm. The ships are not pitched, but rubbed with fish oil. They have one mast, one sail and one rudder, and have no deck, but only a cover spread over the cargo when loaded. This cover consists of hides and on the top of the hides they put horses which they take back to India for sale. They have no iron to make nails of, and for this reason they use only wooden trenails in their ship-building and they stitch the planks with twine, as I have told you. Hence it is a perilous business to go a voyage in one of these ships and many of them are lost, for in that sea of India the storms are often terrible.

If this account is not exaggerated, we can understand that the voyages must indeed have been perilous and the loss of life great

Let us skip the intervening period to the middle of the nineteenth century. In a report of an expedition to the West Indies we find placed before us in a few words a picture of the sickness and fatality which was almost the rule among seamen in those days. At Jamaica in 1741 Admiral Vernon's squadron was greater in complement than at any previous date on this station. During the two years 1740-1, of 15,000 seamen and marines more than 11,000 were sent to hospital and of these there died one in seven. In addition to these (nearly 1600) dying on shore, many of them from yellow fever there were those—their number is not stated—who died on board their own vessels and in two hospital ships.

Much of the sickness which occurred on board naval vessels in the eighteenth century must be ascribed to the evils of the press gang. As men were needed for the Army, so was there a shortage of volunteers for service in the Navy and when more were required 'prestring' was employèd with greater vigour and less discrimination. Prestring was no new procedure, its use for military purposes is traceable back to the days of King John. The term 'prestring' or enlisting by 'prest money,' derives from the French *prêt* = ready, and the 'prested man' meant the 'ready money man,' or, as the recruit was known even in our day, the man who had taken the Queen's shilling, and the recruit was regarded as a volunteer. It is a misinterpretation of modern development to look upon him as a man pressed into the service against his will, analogous to the 'shanghai-ing' of more recent times.

Later, as the country's need for men became more urgent, the net was cast more widely. The freedom of England from attack and the security of the English people were due to the vigilance and activity of the Fleet, which could not, therefore, be allowed to become undermanned. Thereby, many cases of great hardship arose, a man might go out for a casual walk in a seaport town and disappear, the wage-earner would be dragged from his home, his family being left, not merely in ignorance of his whereabouts, but without resources and before them the alternative of starvation or parish relief, such as it was. It was a curious anomaly, the security of the citizens depended on the Fleet, the manning of the Fleet was, therefore, a prime necessity, and the citizens—the prested men among them, at least—were 'made slaves in order to keep them free.'



SIR WILLIAM BURNETT
1779—1861



JAMES LIND
1716—1794



SIR GILBERT BLANE
1749—1834



THOMAS TROTTER
1760—1832

[Photographs from books kindly lent by the Royal Society of Tropical Medicine and Hygiene]

When we come to Pepys's day, 'prestring' had given place to 'pressing,' without even the passing of the King's shilling, gangs were sent out, often with an officer in charge, and with the biblical injunction, "Go ye into the highways and compel them to come in"

Should the supply still be inadequate, as in times of stress it undoubtedly was, application was made to the local magistrates. Some prisoners would accept service more or less voluntarily, to escape the harsh sentences of the day, in other cases convicts were handed over without any option. If the ship was not ready to sail these men might be kept in confinement for some time, and often in a narrow pen. Thus, we read that the 'press room' in Bristol in 1806 was only 8 feet square and into this as many as sixteen men were frequently herded. If more room were needed the men were kept in the local prison to await disposal—"a filthy, evil-smelling hole, crowded with distempered prisoners, without medical care. If they survived [and many, and they the more fortunate, did not] they came out fever-stricken and vermin-covered" to spread disease on board.

Sir Gilbert Blane notes that pressed men are one of the principal means of 'generating and spreading' disease on board, for, he says, they are often of the lowest and dirtiest and have, prior to embarkation, often been kept huddled together in guardships with foul air. To avoid introduction of disease by pressed men Blane advised that they should be stripped and washed, that they should be provided with fresh clothes (there were no uniforms for seamen in those days), their old clothes being destroyed, and that they should have their hair cut before they were permitted to mix with the rest of the ship's company. Doubtless this would guard against the introduction of typhus and relapsing fever and verminous disease in general, and when soon afterwards Sir Charles Middleton, Comptroller of the Navy, saw to this measure being carried out at Portsmouth, the results more than fulfilled expectations.

It was not till about 1833 that the activities of the press gang died out. For a long time it had proved more expensive and more troublesome than the results warranted. We read opinions such as the following, expressed by the captains of the day on the men captured: "Sorry poor creatures that do not earn half the victuals they eat", "Miserable poor creatures, not a seaman amongst them", "Unfit for service and a nuisance to the ship", "Landsmen, boys, incurables and cripples. Sad wretches great part of them are", "All the ragtagg that can be picked up", "Sad thievish creatures", "A hundred and fifty on board, the

greatest part of them sorry fellows", "Twenty-six poor souls, but three of them seamen Ragged and half dead" The causes to which the cessation or suppression of press gangs were ascribed were characteristic, namely, the demoralizing effects of long-continued, violent and indiscriminate pressing upon the Fleet [not from any pity for the unfortunate men pressed], its injurious and exasperating effects upon trade, its antagonizing effect upon the nation and, lastly, the enormous cost as compared with voluntary recruiting

Let us now turn to the conditions of life of the sailor afloat There is little to be said in their favour We shall see shortly that even in the latter half of the eighteenth century, when certain improvements had been instituted, they were none too good, and Sir Gilbert Blane, when writing of the period immediately preceding, said

Sailors in former times had not the attention paid to them which would have been due even to inanimate machines of equal utility, for there seemed to be much more anxiety about preserving arms from rusting and cordage from rotting than about maintaining men in an effective state of health

As late as 1782 he remarked that the supply of 'sope' was new to the service and that the unwonted cleanliness resulting would doubtless find its record in the subsequent reduction in the sickness returns In the following year an increase of fever in one of the West India stations (St Lucia) was ascribed to the importation of recruits newly raised in England, "dirty, ill-clothed and probably harbouring infection," distributed to those ships whose complements were most deficient The fever started in the ships receiving these recruits and spread to others Six of them, when first attacked, were kept apart in one ship, but while still ill were sent to another and thirty of the crew of the second ship caught the infection From the brief description available the disease would appear to have been infective jaundice, Weil's disease, for "the eyes and skin of all that were affected by it became yellow, though without any particular malignancy" Two died on board and one in hospital, an 83 per cent fatality rate We must remember that the ships of those days were heavily rat-infested

The food of the seaman was insufficient and unappetizing In vessels proceeding on long voyages the difficulties of feeding the healthy was great, while feeding the sick was an even greater problem and often no attempt whatever was made to solve it Preservation of food and water, particularly the former, was troublesome even on land, and the difficulties were incomparably

greater on long voyages in tropical heat, and complaints of 'rotten food and reeking water' were common

Three methods of preserving foodstuffs were in vogue, namely, drying, salting, and the carrying of live-stock. The first was used for cod, prunes and apples, the second for meat, fish generally, and vegetables, the live-stock carried comprised chickens, sheep and pigs. Butter was packed in vats as air-tight as possible, and cheeses were preserved, at home by dipping them in boiling fat, at sea by dipping in tar. But the soaking of dried victuals needed more water than could be spared, pickled food would spoil in spite of all precautions, butter became rancid and at times had to be thrown overboard, tarred cheese acquired a disagreeable taste. Flour, groats, rice and bread made from them became stale and weevilly, as did ships' biscuits.

The water was shipped in large tuns or standards of heavy oak capable of resisting flames when sulphured to destroy vermin before they were filled. On a voyage, when the water became foul and odorous, or 'contained too many worms,' a bar of glowing iron or a heated 30-pounder cannon-ball was dropped in. When the stored supply was short, rain would be collected in tarred sails and was said to acquire an after-taste therefrom.

In a list of articles supplied, which I have come across, dated 1719, there were bread, wine, beer, water, beef, pork, peas, oatmeal, butter and cheese, but the beef was usually cooked till it shrunk to less than half—the name 'junk' was applied to it because its texture, digestibility and, we may infer, its nutritive properties, were those of pickled oakum. The pork was often rancid and putrid, as were also the butter and cheese which, we read, had often to be thrown overboard because they 'stank the ship'. The peas 'would not break', though boiled for eight hours they came out 'hard as shotte', the beer would not keep and became 'stinking and sour', according to Sir Walter Raleigh the beer for ships in the days of Queen Elizabeth was stored in old oil and fish casks. Three days a week, Mondays, Wednesdays and Fridays, were known as 'banyan days,' when plum-duff replaced meat. Rice was called by the sailor 'Strike me blind,' convinced as he was that its continued use would cost him his sight [possibly nyctalopia from avitaminosis]. Tobacco was introduced as part of the regular supply in 1798, rum had come earlier, the regular allowance being half a pint morning and evening, this ration being doubled if there was extra work to be done or the weather was bad. In 1740 water was added to the rum by order of Admiral Vernon (the cognomen 'Old Grog,' from the

program coat which the Admiral wore in dirty weather, became transferred from the man to the rum which he watered) We can almost sympathize with the three wishes in a sailor's life "An island of tobacco, a river of rum, and—more rum"

Seamen, said Blane, are to a great extent born, not made, and it is much less expensive to keep the men healthy than to pay for repairing the ravages of disease, the commonest of which were fevers, fluxes, scurvy and ulcers, the last often arising on the smallest scratch Blane was nearer the mark than he knew when he ascribed them vaguely to "the nature of the diet and the malignant influence of the climate"

According to Nelson the life of a man-o'-war's man finished at forty-five years, "racked by agues, distorted by rheumatic pains, ruptured or double ruptured by strain of pulling," a martyr to acute indigestion from the nature of his food, while scurvy was his merciless enemy The surgeons of the day were, with a few outstanding exceptions, a poor lot and their methods crude, while the conditions under which they had to carry on their work were nothing short of appalling Tobias Smollett, a physician of the eighteenth century, notes in *Roderick Random* the quarters allotted to the surgeon's mate in a man-o'-war

We descended by divers ladders to a space as dark as a dungeon, which I understood was immersed several feet under water, being immediately above the holds I had no sooner approached this dismal gulf than my nose was saluted with an intolerable stench of putrefied cheese and rancid butter that issued from an apartment at the foot of the ladder resembling a chandler's shop It was here that the ship's steward gave out provisions for the several messes on board

He goes on to describe the hospital or sick-berth, saying

I was much less surprised that people should die on board than that any sick person should recover Here I saw about fifty miserable distempered wretches, suspended in rows or huddled one upon another, that not more than fourteen inches space was allotted for each with his bed and bedding, and deprived of the light of the day as well as of fresh air, Breathing nothing but a noisome atmosphere of the morbid steams exhaling from their own excrements and diseased bodies, devoured with vermin hatched in the filth that surrounded them, and destitute of every convenience necessary for people in that helpless condition

When his ship was at Carthagena in 1740 we are not surprised to hear that yellow fever appeared on board

The change of atmosphere [he might have added, the situation just above the holds with their stagnant water and bilge], combined with the stench that surrounded us, the heat of the climate, our own cou-

stitutions impoverished by bad provisions and our despair, to introduce the bilious fever among us, which raged with such violence that three-fourths of those whom it invaded died in a deplorable manner, the colour of their skin being, by the extreme putrefaction of the juices, changed into that of soot

Knowledge and instruments were crude, treatment, to say the least, haphazard. Thus, treatment for rupture, from which the majority suffered, was to hang the patient up by his heels until the prolapsus was reduced. Pepys, who was Secretary to the Admiralty, relates that he met a seaman returning from fighting the Dutch and that his eye-socket was 'stopped with oakum'. The old-time naval surgeon excused himself for doing nothing, or perhaps we should say, justified his expectant treatment, by the conviction that "two-thirds had such bad constitutions that no physician could save them, and the rest such good ones that all the physicians in the world could not kill them". Sickness, moreover, was not encouraged. A man taken ill on board, if he did not speedily recover, was put on shore and treated for a month. If he was incurable or was permanently disabled, and was not one of the fortunate few to obtain admission to Greenwich Hospital, he was callously turned adrift to shift as best he could for himself.

Even at the end of the seventeenth century a naval surgeon, Dr Cockburn, had forwarded a complaint that the supply of nourishing food and of cordials for the weak and convalescent was insufficient. By the end of the eighteenth almost the only improvement was the furnishing of a supply of vinegar and the use of raisins in puddings.

The precautions for preventing and avoiding sickness, which were laid down by Blane, could hardly be bettered at the present day, the advantage of the present being that the proposals have been attended to and many of them adopted, whereas in his day and for long after they were allowed to lie on the table. He summed up by saying "Avoid too much exercise in the sun, avoid sleeping in the open air when at infected ports, avoid intemperance in drinking and bad hours". Many fevers, such as jail, ship and hospital fever, *i.e.* typhus, arose from lack of personal cleanliness and the two chief ends in view were to prevent generation of infection on board and introduction of infection from without. He noted that town people were less often attacked than those from the country, owing, as we would say, to some degree of acquired immunity, or, as he put it, because by constant exposure town-dwellers become more used to effluvia, but country people fall ready victims when infection is introduced among

them He notes too that the inhabitants of isolated islands keep in good health until strangers enter carrying infection which may attack most of the islanders We have seen the same in the ravages of introduced disease among Fijians and Samoans in recent times He points out not merely the advantages but the necessity for cleanliness on board and the need of regular inspection to ensure this

A true seaman is generally cleanly [he says (we have seen above how few pressed men were true seamen)], but the greater part of men in a ship of war require a degree of compulsion to make them so they will dispose of their clothes for money to purchase spirituous liquors

He goes on to say that weekly inspection should be instituted and measures to see that the men do not shirk it and that they have clean clothing For this to be done, the men should be allowed one day a week for washing and soap should be supplied in the same way as tobacco (free at that time), in fact soap should be regarded as a necessary supply and tobacco a luxury

The need for ventilation he also stressed and the establishment of air currents by fires The hammocks and bedding should, when possible, be aired by exposure on deck, the latter especially as the beds in those days were often stuffed with chopped rags from old clothes and consequently were liable to be infected

Should infection arise, he advised separation of the sick to a part where each might have more space than in their quarters and where they could be kept from the "idle visits of men in health" Should a patient die his clothing and bedding, if not destroyed, ought to be disinfected by soaking, scrubbing and washing, and the decks, sides and beams of the berths should be washed, scraped, smoked and dried by fire, then sprinkled with hot vinegar and finally be whitewashed with quicklime If many have been sick the whole ship may need disinfection, for this he recommends Lind's method with charcoal, sulphur and nitre This, it will be recognized, was an ancient remedy Ulysses employed it to fumigate the apartments of his palace where the suitors of Penelope had been slain (*Odyssey* X)

For the benefit of convalescents Blane suggested a reserve to be kept by the purser, comprising dried fruits, barley, rice, sago and eggs, "which, if greased and put in salt, may be preserved fresh for a great length of time", also carrots preserved by sugar, green vegetables, preserved by salt, and lemons, oranges, limes and shaddocks, but of the latter particularly lemons

Later additions made to the seaman's dietary were sour kraut and molasses in 1780 for those threatened with scurvy, this was

to replace some of the oatmeal issue Blane gives detailed instructions for preparing burgoo and molasses Prior to this the oatmeal issue had been largely wasted, each man had fully twice as much as he could eat and the excess went to swell the purser's profits Barley was another cereal substituted for some of the oatmeal and potatoes were suggested, but did not become part of the issue till long afterwards For those serving in the West Indies sugar and cocoa were supplied in place of butter, a welcome change for the rancid product of the time

He further recommended ways of treating the drinking water to make it wholesome, notably the addition of quicklime, a pint to each butt, in this amount he maintains that it is not injurious to health, "but, on the contrary, is rather friendly to the bowels, tending to prevent and check fluxes," and also inhibits the growth that collects on the surface of the water and on the sides of the casks, "called by naturalists *algæ*" He had also heard of purification by filtration through a drystone, and mentions Lind's sand-barrel filter If no proper apparatus is available for distilling sea-water, such as a head and worm adaptable to the common boiler, Lind had a contrivance by which a tea-kettle with the handle removed was inverted on the boiler and a gun-barrel fitted to the spout passing through a cask of water as a cooler or kept constantly moist by means of a mop

Blane next takes up the matter of *clothing* Hitherto, though officers had uniforms, the men wore anything they liked, usually the verminous rags in which they were brought on board "It would be," he says, "for the benefit of the service that a uniform should be established for the common men as well as for the officers" If this were done not only would they be better clothed, but they would not be at liberty to sell their clothes for liquor, and they would not bring on board infected clothing When they go on shore they should be given shoes (I still quote Blane) When men first entered the service—that is the volunteers, for the privilege did not apply to pressed men who usually needed it more—an advance of two months' wages was given to them to provide themselves with necessaries Naturally, the men's idea of what constituted necessaries would not coincide with that of those in authority and, moreover, the amount was quite inadequate for a long voyage with exposure to rough work and all weathers For replenishing, the men could often not obtain what was their due, for there was a widespread, almost generalized, system of 'withhold the pay and keep the man' This, however, was bad policy as well as bad morality, for the men had little or nothing

to lose by desertion. If certain articles were regarded as necessities and were provided for the men gratuitously in the first instance and of standard material—shirts, trousers, hats and boots—the Government, Blane averred, would gain in the long run by preserving the men in better health and so save in expense of hospital treatment.

He considers also the question of the men's *duties* and suggests dividing the ship's company into three watches, since by the customary routine of watch and watch about, there are more men on watch at a time than are needed for the work, especially at night, those below get only four hours for sleep, rest and refreshment, and this is not long enough for their clothes to dry if they have been exposed to wet, while those on watch, their work done, will lie about on deck and get chilled.

He even recommends a reversion to former methods of naval construction, particularly for frigates which prior to his time had the kitchen between decks. Later this was changed and it was placed under the forecastle and the heat and smoke would not diffuse through the ship and set up a draught of purifying air. With the older, centrally placed fire, there was better ventilation and the men were more comfortable. For ventilation of lower decks and holds windsails should be set up. The ballast in those days was usually sand and earth, he suggested shingle, *i.e.* pebbles, instead, as the former soaked up and retained moisture and collected filth.

Blane sums up his recommendations by saying that it is cheaper to keep men well than to support them in invalidism and replace the sick.

It is the character of seamen to be thoughtless and neglectful of their own interest and welfare, requiring to be tended like children, but from their bravery, utility and other good qualities, they seem entitled to a degree of *parental* tenderness and attention from the state they protect and the officers they obey.

In October 1781, Blane presented a memorial to the Board of Admiralty, for preventing sickness and mortality among seamen in the West Indies. The main theses which he put forward were—

1 Officers should inspect the men and their clothing weekly. This should be a regular duty and not a measure left, as it was at that time, at the discretion of officers.

2 There should be a supply of fruits and especially of lemons, to this end small vessels should be engaged to collect the fruits at different islands and furnish the ships. At the time such articles were purchased by the ships when they put into port and

it was not possible to take sufficient for any long voyage. He also suggested that wine should be supplied in place of spirits (rum) as the regular ration.

3 Better provision should be made for the sick, without additional expense to the patients. In his day, though men might be sick, the ordinary amount of salt meat and other victuals was served out. Though the quality might be poor or even bad the quantity was more than each man required and when a certain number were sick the quantity was, of course, in still greater excess. This was either used by the seamen who did not want it or, more usually, was thrown away.

4 He affirmed that surgeons "could not do justice to the men without wronging themselves." It would appear that a certain amount of money was allowed to the surgeons who spent it as they wished, the price of instruments and of drugs was often high, so the surgeons would purchase a minimum of necessities. Blane suggested that the Government should supply gratuitously some at least of the articles, in particular Peruvian bark.

5 Accommodation for the sick in hospitals on shore was often worse even than on board, from the overcrowding, bad ventilation, and foul air fresh contagion was frequently contracted there. He suggested that in shore hospitals there should be better spacing of beds, that infectious patients should be separated, and that hospital ships should be established. He remarked that in a single year in the West Indies, among 12,109 men there were 1518 deaths from disease, apart from 150 invalided.

Blane gives in an appendix to his book a list of articles, divided into 'principal' and 'secondary,' with which a surgeon should provide himself, because (these are his own words) "the printed list of articles with which the Navy surgeons are enjoined to supply themselves is very injudicious considering the present improved state of the medical art." He includes, in accordance with his Memorial to the Admiralty, "necessaries to be put in charge of the Purser and served out to the sick in place of common sea provisions."

His Memorial evidently attained part at least of its objects, for in the following year he notes that the squadron had been supplied by the Commissioners of Victualling with "most of the articles recommended, in such quantities as to prove their efficacy" and that the health of the men had improved. "No man," he writes, "died of disease from December 1781 to May 1782, and only thirteen were sent to hospitals whose complaints were small-pox and ulcers." In the previous May and June three died from

disease on his ship alone and seventeen were sent to hospital on account of infection contracted on board

In order to show that the evils referred to were more than merely local, a few more opinions of naval authorities of the latter part of the eighteenth century may be given. Sir John Jervis states "The civil branch of the Navy was rotten to the core", Admiral Sir Vesey Hamilton "The iniquity and corruption were almost incredible". It could not very well be otherwise when we remember that in those days commissions were obtainable by purchase and men were naturally seeking wealth and emoluments, commercial morality was not of a high standard, food was bad, pay worse, the men's quarters were, as we have seen, damp, unhealthy, devoid of comfort, crews were partly pressed men and recruited generally from the dregs of humanity, brought on board by no means infrequently bound hand and foot, while the band played one of the favourite airs of the day, without any thought of its ironical application. "Who are so free as the sons of the sea?" Officers were often severe to the point of brutality, their manners as rough as their speech and as forceful, human life was held cheaply and the men driven to crimes and breaches of the inhuman discipline of the Navy of the middle and later years of the century. Food was bad, drinking water foul and slimy, sanitary arrangements [save the mark!] were appalling and the code of morals so low as to be almost non-existent.

But the picture was not uniformly sombre, there were good and humane commanders such as Captain Cook, there were men such as Bligh of the *Bounty*, bold, intrepid, stern, but not, I think, wantonly cruel, who could sail a boat only 23 feet long, with nineteen men on board, with 7 inches only of freeboard, a journey of 3618 miles, on very short rations, and lose only one man, John Norton the quartermaster, and him not by disease or privation, he was killed early on the voyage by hostile natives.

We in these days can hardly conceive the conditions of those times, however clear and detailed the description. Navigators with a rough, rebellious crew would explore uncharted seas in vessels no larger than a fair-sized yacht. Cook made the first of his three famous voyages in the *Endeavour*, 370 tons only, with a complement of eighty-four. Nevertheless there was no sickness on board until they arrived at Batavia where so many fell ill that they were delayed for some months. The cause seems to have been dysentery, for he states

We were fortunate to lose but few men at Batavia, but in our passage thence to the Cape of Good Hope we had twenty-four men

died [a third of the ship's complement]—all, or most of them, of the bloody flux. The fatal disorder reigned in the ship with such obstinacy that medicine, however skilfully administered, had not the least effect.

Batavia had an ill repute at that time. Barron, in an account of a voyage to Cochin China in H M S *Lion*, says

The mortality of the Europeans in Batavia is far beyond what is known in any other settlement, exceeding those in the most fatal of the West India Islands. We had indeed in our own instance a fatal proof of the malignancy of the climate, notwithstanding every precaution that was taken for preserving the health of the crew. A dysentery, accompanied with typhus fever, was here brought on board, which continued with more or less severity during the remaining part of the voyage. We had not lost a man on our arrival at this place, but from hence to the end of the voyage there died not fewer than fifty men.

This sounds like dysentery and enteric fever. The story of Cook's Second Voyage in H M S *Resolution*, of 462 tons, with that of the accompanying ship, the *Adventure*, of 336 tons, in 1772-5 really belongs to the epic of scurvy, the second vessel's voyage being regarded as a control to the experiment of the first, but it may be told briefly here.

In those days a voyage of six weeks or even a month practically always implied an outbreak of scurvy.

A graphic account is given in Magellan's history of his voyage of circumnavigation, two and a half centuries before Cook. The original version, in Italian, appeared in 1536. He states

Wednesday, the 28th of November, 1520, we entered the Pacific sea, where we remained three months and twenty days without taking in provisions or other refreshments, and we ate only old biscuit reduced to powder, and full of grubs, and stinking from the dirt which the rats had made on it when eating the good biscuit, and we drank water that was yellow and stinking. We also ate the ox-hides which were under the main-yard, so that the yard should not break the rigging. They were very hard on account of the sun, rain and wind, and we left them for four or five days in the sea, and then put them a little on the embers, and so ate them, also the sawdust of wood, and rats

but enough of these could not be got. Besides the above-named evils, this misfortune which I will mention was the worst, it was that the upper and lower gums of most of our men grew so much that they could not eat, and in this way so many suffered that nineteen died.

In contrast with this Cook writes from Dusky Bay, New Zealand, that

they had now been 117 days at sea, in which time they sailed 3660 leagues without having once sight of land. It is but reasonable to think that many of the people must be ill of the scurvy. The con-

trary, however, happened Sweetwort had been given to such as were scorbutic This had so far the desired effect, that they had only one man on board that could be called very ill of this disease

They left a few goats and sheep which, after the long voyage, were expected to devour the grass greedily, but to their surprise the animals would not taste it On examination, it was found that their mouths were sore, gums swollen, teeth loose, in short *they* showed the symptoms of scurvy, whereas the men did not

Captain Cook knew that in Queen Charlotte's Sound he could obtain scurvy grass (*Cochlearia officinalis*), celery and other vegetables He did so and gave orders for these to be made into soup "with wheat and portable broth" and this was given every morning for breakfast and again with pease and broth for dinner The *Adventure*, whose captain either did not know or did not enforce these precautions, affords a remarkable contrast "The crew was sickly Her cook was dead and about twenty of her best men were down with the scurvy and flux" Cook's own ship had only three on the sick-list and only one with scurvy Several more of the *Adventure* began to show symptoms of it, but were cured when given "the wort, marmalade of carrots and rob of lemons and oranges"

Cook quaintly remarks

To introduce a new article of food among seamen, let it be ever so much for their good, requires both the authority and example of a commander Many, officers as well as seamen, at first disliked celery, scurvy grass, etc being boiled in the pease and wheat, and some refused to eat it

Since, however, this had no effect on the Captain's own conduct "the obstinate kind of prejudice by little and little wore off and they began to like it as well as the others"

In his summing up of this voyage he notes that they were away from England for three years and eighteen days, under all changes of climate and lost only four men altogether, and only one of these on account of sickness, because

The men were furnished with a quantity of malt with which they made Sweet-wort Any showing symptoms of scurvy was given 1-3 pints daily of this Sour krout, of which they had a large quantity, was found highly antiscorbutic and did not spoil from being kept Each man while at sea had a pound of this twice a week or oftener

At the same time Captain Cook took care that other measures for the men's comfort and welfare should not be neglected Every effort was made to keep the men, their clothes, hammocks and bedding dry Weekly or at times twice a week, the ship was

aired with fires, when this could not be done the less pleasant procedure of smoking the ship with gunpowder mixed with vinegar or water was substituted. He ends by saying, "Our having discovered the possibility of preserving health amongst a numerous ship's company for such a length of time, in such varieties of climate and amidst such continued hardships and fatigues, will make this voyage remarkable"—a fact borne out by history.

Captain Cook's Third Voyage, 1776-80, is little known as regards its medical aspect, the whole being overshadowed by the fact of his death at the hands of the natives at Kakooa. We find, however, reference to yet another antiscorbutic, obtained at Samganoodha Harbour. Here he found great quantities of berries and one-third of his crew had leave by turns to go ashore and pick them. They also obtained by purchase or barter considerable quantities from the natives. "If there were any seeds of the scurvy in either ship (the *Resolution* or the *Discovery*) those berries and the use of spruce beer which they had to drink every other day effectually eradicated them." [Captain Charles Clerke, who succeeded to the command on the death of Captain Cook, himself died on 22nd August, 1779, at the age of 38 years, from consumption, signs of which were present before he left England and from which infection he suffered lingeringly till near the end of the voyage.] On arrival home, the then commander reported

In the course of our voyage the *Resolution* lost but five men by sickness, three of whom were in a precarious state of health at our departure from England. The *Discovery* did not lose a man. Unremitting attention to the regulations established by Captain Cook may justly be considered as the principal cause.

The voyage had lasted 4 years 2 months and 22 days.

Another experiment had been carried out during this last voyage, about which little seems to be known. At the beginning of the voyage, biscuit, flour, peas, oatmeal and groats had been sealed up in small casks lined with tinfoil. On arrival of the vessels at home again these were opened and "we found all except the pease, in a much better state than could have been expected in the usual manner of package." Considering that no means of sterilization had been carried out prior to the sealing this is indeed a surprising and noteworthy fact.

This is a convenient place to add a few words on the preservation of food by bottling and tinning or 'canning,' for it was about this time or soon after that Nicholas Appert was experimenting at Massy (Seine-et-Oise) on his process of preserving food by placing it in bottles, securely stoppering and subjecting the whole to

'boiling water in a water-bath' He used glass bottles and, ruled by the idea then current that putrefaction was due to contact with air, laid stress on the efficient stoppering before heating

In 1810 his work appeared with the title *Le Livre de tous les Ménages ou l'Art de Conserver pendant Plusieurs Années Toutes les Substances Animales et Végétales*

He thus preserved beef, mutton, veal, vegetables, soup and *bouilli*, the name being corrupted by sailors to 'bully-beef' Iron and tin containers for preserving foods were patented by Augustus de Heine (February 1810) and Peter Durand (August 1810) The products were tested by hermetically sealing and exposing in a test-chamber for a month or more to a temperature of 90–110° F Putrefaction (and therefore imperfect sterilization) was evidenced by bulging of the containers (*Encycl Brit*, 1841)

In the final account of Captain Cook's third voyage there is a recommendation that a sufficient quantity of Peruvian bark should be given to such of His Majesty's ships as may be exposed to unwholesome climates The allowance at the time was clearly most inadequate The report states

Fortunately only one of the men in the *Discovery* needed this when he had fever in the Straits of Sunda and he alone consumed the total quantity carried in such vessels as ours Had more been affected in the same manner, they would probably all have perished from the want of the only remedy capable of affording them effectual relief

We now come to the beginning of the nineteenth century and for our knowledge of the conditions of the seamen in the Navy of that period we are largely indebted to Thomas Trotter We find that in spite of Sir Gilbert Blane's Memorial to the Admiralty, in spite of all that Lind had done and that Cook had demonstrated, the change in the surgeon's department had not been great Trotter writes

In the first ship where I was surgeon's mate I remember a sick-berth half-inclosed with hammocks being fixed near the galley, more with a view to stifle contagion with the smoke from the fire than to keep the patient comfortable

Lind's doctrine of fumigation [we shall see later what Trotter thought of fumigation] was then in full vigour, to which our captain, like all others, bowed with submission If, however, by this means infection was roasted to a cinder, the poor sick man was often in danger of losing his eyes from the wood-smoke in undergoing this fiery ordeal

A considerable step in advance was made when the 'improved sick-berth' as devised by Captain Markham of the *Centaur* was adopted This took in the two foremost guns under the fore-castle,

and thus included the round house and head-door and the mid-ships formerly occupied by a pigsty. Over the latter part was a large skylight which added considerably to the general brightening and in warm weather this could be thrown open for ventilation. An additional advantage was that patients could be examined in daylight instead of the murkiness and more than semi-obscurity of the 'tween decks prior to this. Trotter remarks that

it is of much consequence in particular diseases, such as the accession of typhus, to see the countenance by daylight, the very cast of the eye and the hue of the face are leading characteristics of early infection. I trust the service will never again relapse into the slovenly habit of dressing or examining the sick in a cockpit.

The Markham sickberth in the larger vessels allowed room for twenty-two bed patients and if more space was required a temporary berth for convalescents could be erected on the opposite side without difficulty.

The following seems strange to our modern ideas, the seaman of to-day will probably regard the present conditions as a retrogression from the former comforts in this respect, though doubtless it interfered with their freedom in foreign ports.

During the war [writes Trotter] it has been much the practice to carry a number of the most orderly married women to sea with their husbands. Many of these have lain in on board, a commodious apartment being always fitted up for the purpose, where the puerperal female has such comforts as scarcely to be met with in any lying-in hospital in England. I have known five births in the space of a month in a single ship, had the poor women been left to other charities, it is probable many of both mothers and infants must have perished. Our surgeons by these means have had a larger practice in midwifery than falls to the share of some accoucheurs on land. It is surprising to see the number of fine children that have been born on board. The officers and ship's company on these occasions make subscriptions for the mother and infant, which always exceed much what is required, and often enables the husband to send his wife home in a stage-coach.

Under circumstances where wounds often became infected with *Bacillus tetani* and no antiseptics was employed, one wonders what were the maternal and infant mortality rates.

Trotter, like Blane, worked hard to improve the lot of the seaman and the conditions of his service. In 1799 he made application that the bedding of seamen might be scoured—the fleet was in harbour at the time—but was informed that the expense, sixpence a pair for blankets, would be too great. He wrote again the same year complaining that on his visiting Torbay Hospital the third day after the sick had been landed eleven patients in one ward were still without sheets, though the hospital was only

a little more than one-third full He was informed that the matron was getting the sheets ready 'as fast as possible'

The following year he complains, as doubtless many a modern naval medical officer does, though, unlike Trotter, he rarely dares to commit his complaint to writing, regarding interference of the larty in high places with matters strictly medical He quotes a circular memorandum from Lord St Vincent which reads as follows

Confident as the Commander in Chief is that many consumptive cases might be prevented and others mitigated by timely application of flannel next the skin in catarrhs, coughs and common colds, he most seriously exhorts the captains of ships comprising the fleet under his command to inculcate this doctrine in the minds of their surgeons who from *caprice* and *perverse opposition* to every wholesome regulation grossly neglect this important duty (Dated, 13th October, 1800)

Jennerian vaccination was being carried out with much success and met with little if any opposition, "the seamen willingly submit and Mr Dunning of Plymouth Dock, a disciple of Jenner, kindly supplies our surgeons with recent vaccine matter from his numerous patients"

The next year (1801) Trotter and more than eighty others subscribed for a naval gold medal which he presented to Jenner [it is illustrated in Trotter's book, v III, p 121] In this year, too, he made proposals to Lord St Vincent for ameliorating the lot of naval medical officers whose remuneration and prospects were far below those of the Army, he suggested the appointment of two inspectors of health in direct communication with the Admiralty whose duties would include inspection of all naval hospitals, guard-ships, convalescent ships, prisons and prison-ships I have not been able to find out what success his proposals met with The lot of men admitted to hospital needed improvement In 1802, reporting upon the state of things in Plymouth Hospital, he wrote "The war is over and no operation room has yet been fitted to this hospital It is not decent to operate in a full ward where the cries of the patient offend others"

Risks of introduction of infection into ships were in his day great and unnecessarily so Newly commissioned ships received as their complement raw landsmen, drafts from crowded guard-ships, pressed men, convicts, many of whom, as already shown, were carrying disease or harbouring the vectors of infection This was well known and consequently, when possible, such men were generally employed at first on home stations, but in time of war, or when expeditions were setting out, this was not feasible Trotter

is very insistent on the provision of baths and expresses surprise that none are found on board for regular bathing of men, or even officers. It is true that if they had been provided the men would probably have objected to using them regularly, for he remarks that when he was at Haslar, though "there were tubs such as were used in slop ships for purifying new-raised men, the seamen had such a dislike to them," but this was probably because of the association, for he adds "a sailor under disease ought to be bathed like a gentleman."

He is strongly averse to 'pressed men,' partly, if not mainly, on account of their introducing disease. Impressment of seamen, he says, should not be called a necessary and politic measure for the safety of the country, but a most fatal and impolitic practice, for it was the cause of more destruction of life and deterioration of health among seamen than all other causes. He calls attention in his three-volume work *Medica Nautica* to a matter which, one would think, was obvious and of the first importance, as if it were a remarkable suggestion, that men when first appointed to a ship should be thoroughly examined so that "disordered and infectious or foul ulcerous persons may not be admitted." He is much in favour of Pitt's Act (1795) for *requisition* of seamen and landmen for the Navy. This, unfortunately, was only a temporary measure. Had it been made permanent counties and towns could have been called upon for levying men when such became necessary, that is recruiting them as volunteers, when they would come up reconciled to their lot and not on the look out for opportunities to desert. He, too, is in favour of provision of proper uniform "of decent material provided by Government," in which the men would take pride while it would make desertion more difficult. He gives an example of the dangers of sending men on board without discrimination or proper examination.

This day one man in smallpox and another in measles, both in a state of eruption, were sent on board the *Charon* from the *Gibraltar*. These diseases did not extend to any other persons. Six seamen and the gunner's child were inoculated, in consequence on board the hospital ship, all of whom had the disease in the mildest degree.

He says nothing regarding the measles case and whether he infected others, there was no prophylaxis then.

It was not only to perils from their own countrymen that seamen of those days were exposed. Trotter notes how that on 1st June 1791 on the taking of some French ships many of the crews of the latter were ill and "from being dirty to an extreme degree, a contagious fever had carried off many." The English

ships making the captures and taking these men on board became infected with typhus Trotter had not much faith in disinfection, in fact at times he ridicules it and waxes sarcastic on the subject. Speaking of the disease thus conveyed to the English ships by French prisoners he writes

Those officers who had confidence in fumigation performed it every morning the decks were kept clean and the whole inside whitewashed constant attention was paid to the cleanliness of the people's cloaths and the bedding was spread abroad every day to air The seamen were ordered to keep themselves clean in their persons and to shift [change their underclothes ?] more frequently Fires were kindled in pots in the hold, well and bread-room, stoves in the orlops, cabletiers, and fore and after cockpits

Immediate separation of those infected, however, he thought was a more dependable measure, care being taken to remove even very mild cases Nevertheless, the disease caused a good deal of havoc Nurses and attendants on the prisoners and numbers of the Middlesex Militia on guard over them were attacked with typhus, 800 cases were sent to Haslar and forty patients (5 per cent) died—not a high fatality rate Similar reports were sent from other ships present in the engagement or on which prisoners were brought The disease was undoubtedly typhus, but was reported under various names *Febris nautica*, *Febris putrida*, *Febris maligna*, *Febris petechialis*, *Purple fever*

By order of Earl Howe, Dr Trotter visited also the Portuguese squadron and found a contagious fever prevailing there "The officers as well as the men are accustomed to lie down in bed with their clothes on" To go from one of their ships to an English man-o'-war was "like coming from a sepulchre to a banquet" and we have just seen that the state of the English ships left a good deal to be desired On one British ship, the *Europe*, were 500 people in different stages of fever, one part of the vessel after another being appropriated for them The Portuguese, one would think, could hardly be in a more parlous state

Disinfection for typhus on board was, to say the least, drastic, Dr Smyth's method being employed The account is worth quoting in his own words

Every man was ordered below, the scuttles close shut, tarpaulins laid over for half an hour, during which time nitrous gas was dissipated through the ship, according to the directions given in Dr Smyth's Pamphlet Very soon after it was begun to be used, a number of men were affected with coughing, and before the half hour was expired the coughing became more general and in many attended with head-ach, which did not leave them till after walking the deck in the free air for a considerable time

Next day he continues

Dr Smyth's process was repeated and attended with the same effects as yesterday which, in my opinion from the irritation produced in the lungs, is a proof that it is in some degree unfavourable to respiration

With this, there is little doubt, all will agree

Speaking of the same disease, typhus, he says that the washerwomen at Haslar know when a dangerous disease is prevalent in the hospital from the bad smell of the clothes, before washing them they expose them to the air until the smell goes and they can then wash them in safety We know now that this means that exposure to cold caused the lice to leave the clothes and so removed the vector He notes that contagious fever, *ie* typhus, is not a disease of negroes, he means, of course, in their native state, because they do not wear clothes and therefore are not liable to "the filth and uncleanness which generate infection" We must remember also that louse-borne exanthematic typhus is a disease generally of colder climates

Reverting once more to Trotter's views on disinfection he thinks, and probably with good reason, that disinfection as carried out in his day was merely masking or replacing one odour by another and that what was needed was fresh air, not more contaminated air Smyth's 'nitrous method' had been directed by official authority to be employed for destroying contagion throughout the British Navy Trotter regards it as "a relict of the old animalcular hypothesis of contagion" Supported by American investigators, Mitchell in particular, on whose opinion he has great reliance, he scorns 'acid fumigation' and agrees that *alkaline* bodies are the only sound remedies, preventives and antibodies The argument forms interesting reading into which we cannot go here By ventilation you admit pure air, by fumigation you introduce foul air, says Trotter In a circular letter as Physician of the Fleet he urges surgeons to continue in firm opposition to 'unrespirable gases,' such as septone, azote or nitrogene, as correctors of contagion, he agrees with certain American investigators that nitrous gas is worse than useless, it is harmful because, he dogmatically states, "the cause of contagion and of many endemic and epidemic diseases is some chemical combination of septone with oxygen" He ends with these words

Fumigation has had a long reign in the practice of physic it has slain its thousands and ten thousands There is a rising generation of surgeons in the British Navy, who are capable of wielding the principles of science, and they will never again suffer it to walk the earth *Peace to its Manes!*

Later he took more drastic steps when he says . " Fumigation was being carried out by Dr Smyth's method, 'but I stopped the idle waste of saltpetre "

Conditions in the Mercantile Marine in those days were, though it seems incredible and hardly possible, even worse . It is to us a matter for wonder that anyone entered it, or, having inadvertently done so, did not seize the first opportunity to escape . Press-gangs and gaol-birds could help to maintain the personnel of the Navy, but the merchant service had no such stay . Early in the seventeenth century an East India Company's surgeon, John Woodall, published *The Surgeon's Mate*, in which is to be found much sound advice, expressed in somewhat quaint diction . In his day some attention at least was paid to the sailors' well-being, but later matters became worse and their state nothing short of deplorable . The lot of the medical officer on those vessels that carried one was far from happy . The East India Company had a Marine Medical Service for the medical requirements of their ships' personnel . Here is an example of the kind of treatment they might have to put up with . One medical officer in 1695 lodged a complaint against the Captain of the ship on account of ill-treatment, which included beating with a cutlass and a ducking [he means keel-hauling], " which is the next punishment to death " . Another, more than a hundred and twenty years afterwards, in 1818, was kept in irons for twenty-one days for whistling on the quarter-deck, in the presence of the Captain, after being told to desist !

So little was known of tropical diseases that faced by the high morbidity of some foreign stations medical officers were reduced almost to despair and most of them did very little . Bryson published in 1847 a report, at the instigation of Sir William Burnett (1779-1861), the Medical Director-General of the Navy at the time, on the *Climate and Principal Diseases of the African Station*, from which it is seen that the Coast had a bad record . He tells how that for the twenty-one years, 1825-45, the death-rate per mille was 54·4 as compared with South America 7·7, Mediterranean 9·3, East Indies 15·1, and West Indies 18·1 . It was Sir William Burnett who in 1827 made arrangements for the instruction of medical officers in the Navy, but it was not till more than another half-century had passed that, in 1881, the school at Haslar was started for teaching general and naval hygiene and it was only in 1900 that tropical diseases and their study were added .

Naval medical officers did their very best to get the conditions

on ships ameliorated and the want of success to obtain remedies for the most obvious defects must have been terribly disheartening. We have spoken of Blane and Trotter, but before either of them came James Lind (1716-94) who served in the Navy and at Haslar from 1739 to 1754. There were two physicians named James Lind, both were famous and they were contemporaries. One was the naval physician who lived from 1716 to 1794 and was Physician to the Royal Hospital, Haslar, and wrote the work on Scurvy, but had no experience in India, though he published a treatise on Tropical Medicine in 1768. The other lived from 1736 to 1812, was Physician to the Royal Household at Windsor, was a Fellow of the Royal Society, and was in Bengal in 1762. It is to the former that we refer here. Many of his recommendations made on empirical grounds or on the results of his personal observations found scientific confirmation and proof a century or more afterwards. In his *Precautions in Southern Climates* he lays stress on the importance of anchoring away from swamps, on avoiding night air, on keeping the gun-ports closed at night, on screening by sails, on the use of smoke, on the utilization of off-shore floating 'factories' (as he called them) on which people could live and remain healthy even on the West African Coast are all so sound that, as we have written elsewhere, one wonders he did not stumble on the mosquito to man relationship of malaria fever. He advocates drachm doses of bitter infusion of bark morning and evening, *i.e.* quinine prophylaxis. In ships at so-called healthy stations and in hospitals at home receiving the sick from vessels returning from abroad the amount of disease was truly appalling. Lind, when at Haslar, writes that in the two years 1758-60 there were 5743 patients admitted to the hospital, among them 2174 with fevers, 1146 with scurvy, 53 with smallpox and 30 with leprosy. To his greater honour be it said that he was an enthusiast for prevention at a time when large hospitals were built at great cost and were kept filled mainly with cases of preventable disease. In spite of all Lind wrote and urged, of his epochal work on scurvy published in 1754, of the success of his methods applied by Captain Cook in 1772-5, lemon juice was not a compulsory issue in the British Navy until 1844. Though lemon juice has an antiscorbutic potency four times as great as that of limes, nevertheless in 1860 the latter was allowed to replace the former. Of Lind, Blane and Trotter it has been said

They struggled against stupidity and ignorance, prejudice and indifference in high places and low, the Admiralty and the fore-castle, they had the hard task of seeking to break down immemorial custom,

dared to challenge tradition, hammered at the walls of a hierarchy as soul-chilling, as rigorous, as iron-bound as any Brahmin caste, preached seemingly frivolous novelties to insular conservatism that held hardship essential for hardihood

Let us now pass to the present century and note how Naval and Marine Hygiene came to be based on scientific foundations and the construction of ships altered to enable these essentials to be applied

Crew accommodation from the close quarters below the water-line was established in a deck-house, but this, we must confess, did not become so common on British vessels, except those of the better class, and was not adopted so early as on Danish and Norwegian merchantmen. Even then there were defects, not yet done away with, of insufficient height, light and ventilation, means of heating are also inadequate. Overcrowding is not usually an evil, because for economy's sake the tendency is to underman, particularly in the days of steam and still more in oil-ships.

When iron vessels came moisture would condense from the air of the crews' quarters on the sides and beams, the whole space became damp and water dropped on to the bunks. This was remedied by covering the metal with wood or dusting granulated cork on the surface after varnishing, this, however, though remedying the trouble from excessive moisture was not an un-mixed blessing as the sheathing was liable to harbour dirt and vermin.

The *sick-bay* in the modern battleship occupies the midship part of the main deck, lighted and ventilated from above. In some it is placed on the upper deck within the superstructure and is naturally ventilated, in smaller vessels it lies forward on the main or lower deck.

The air in the lower parts of cargo boats is apt to become foul and humid from ill-ventilation, burning of oil lamps or candles, shipping seas, from decomposing organic matter in the bilges, effluvia from cargo, especially on cattle-boats and those carrying grain, guano, bones, compressed fuel and such-like, and, finally, gases evolve from coal-bunkers and raise the temperature. By a Board of Trade regulation "every place occupied by seamen shall as far as practicable be shut off and protected from effluvia which may be caused by cargo or bilge-water."

It will not be unprofitable and may help to bring more clearly before our minds the conditions under which the majority of sea-

men live to-day, if we compare their accommodation at sea with that which holds good for people on land. Firstly, unfit dwellings on land can be demolished, either individually or collectively, under Town Planning and Housing Schemes. Overcrowding can be drastically dealt with, there being a legal minimum of 50 sq ft and 400 cu ft for each person over ten years of age in inhabited rooms. In seamen's lodging houses a lower minimum is allowed, 36 sq ft and 300 cu ft. In ships the legal minimum is still 15 sq. ft and 120 cu ft, including messroom, bathrooms and lavatories. Further, can we imagine any Local Authority, having demolished old houses, building new ones which reproduce all the disadvantages of the old? That there are exceptions we shall see in the account below of the most modern accommodation at sea, recently reported, but these remarks apply to the generality of shipbuilders even to-day.

Ashore the Ministry of Health looks after the health of workers in their homes, the Home Office safeguards them in the factories, and each has a strong medical department, is it not an anomaly that in the Board of Trade, which looks after the living and working conditions of seamen, there is no such medical representation?

The stereotyped argument that it is useless to provide better accommodation because the men would not appreciate it is not valid, nor is it accepted with respect to rehousing ashore, and we should not forget that tuberculosis is the chief factor in maintaining a high morbidity and death-rate among seamen.

One of the Twenty-five Recommendations of the Association of Port Sanitary Authorities is to the effect that when plans for new ships are under consideration the accommodation proposed for officers and crews should be approved by a committee of which at least one member is a medical sanitarian with a special knowledge of marine hygiene. If this is adopted and acted upon it would go further than all the other twenty-four in bringing about improvement in new quarters.

Ventilation now has to be as far as possible (but often it is not possible) natural, otherwise hatchways, skylights, ports, scuttles, windsails have to be utilized, or hollow iron masts or the funnel casing are brought into play. Adaptation of Hales's ventilator to ships had been recommended in the middle of the eighteenth century. On small vessels the difficulty is greater because, as regards the men's quarters, the only inlet and outlet for the lower forecabin is the hatchway which in stormy weather the occupants naturally keep closed. In modern vessels propulsion

methods are used, those employing extraction are not so satisfactory, owing to the complicated structure of the interior of the ship. As this is not a work on naval construction, we need only enumerate, not describe, the methods employed to-day in the artificial ventilation of ships, such as by pipes from the holds opening beneath or over fires, exhaust pipes in the funnel casing, Edmunds's steam-jets or gas-jets discharging into exhaust pipes, air pumps, cowls fitted to exhaust pipes while fresh air is introduced by Boyle's system of downcast ventilators, by Green's system of jets of compressed air discharging into the main air-trunk, Perkin's automatic exhaust, and rotary fans.

The *water-supply* for ships in the old days was obtained in casks or barrels from the shore and those engaged in this duty often fell sick. Blane states that men would be sent ashore and having filled the receptacles would leave them there all night with men to watch them. At the watering-place at Rockfort, Jamaica, which he particularizes [the present author knows it well], there is a land breeze at night which blows over ponds and marshes and hardly any of the men remaining to guard the casks escaped fever and some died of it. The crews of ships who did not follow this practice remained free from infection. "Probably something caught or imbibed [we are reminded here of Manson's idea that malaria was caught from drinking water containing the bodies of mosquitoes which had died after ovipositing] is the cause of the fever, for it lies for some time inactive in the constitution, some of the men not being affected for more than a week after they had been at sea" [the incubation period of malaria we know to be about eleven days]. Blane makes a similar statement that the air of ships is healthy whereas that of the land is not, especially near marshes. He is strongly in favour, therefore, of having wooding and watering done as much as possible by local negroes who are immune. [It is strange to meet this word in this connection written so long ago.] If men have to go on shore in the evening to collect wood or water he urges that they should be given protection by the regular use of Peruvian bark, he found that it was good even after such exposure because he noted that there was an interval of ten days to a fortnight between "inhibition of the noxious principle whatever it is" and the onset of attack, as has already been remarked. There was always the risk also of bringing mosquito eggs, larvæ or pupæ on board with the water. When the amount taken on board in this way was insufficient, or when it became foul and undrinkable, as it not infrequently

did as the casks and barrels were not cleaned, some process of distilling sea water was employed. The discovery that fresh water can be obtained by distillation of sea water has been attributed to Lind, this is erroneous. He was forestalled at least a century and a half by Sir Richard Hawkins who, when writing of the voyage of the *Dainty* in the South Seas in 1593, says

In the passage to Brazil our fresh water had failed us many days by reason of our long navigation, yet with an invention I had in my ship I easily drew out of the water of the sea sufficient quantity of fresh water to sustain my people with little expense of fuel, for with four billets I stilled a hogshhead of water and therewith dressed meats for the sick and hale. The water so distilled was found to be wholesome and nourishing.

Captain Cook in his second voyage, 1772-5, having run short of water, ordered a still to be fitted to the largest copper which had a capacity of over sixty gallons. He tells how the fire was lighted at four o'clock in the morning and the still began to run in two hours. The process was kept up till 6 p.m. by which time they had distilled thirty-two gallons of fresh water, using one-and-a-half bushels of coals. In spite of its usefulness Captain Cook advises that no man trust wholly to it, for

although you may, provided you have plenty of fuel and good coppers, obtain as much water as will support life, you cannot with all your efforts, obtain sufficient to support health, in hot climates especially, where it is the most wanting.

Moseley, apparently unaware of these records of Hawkins, of Cook, and of Lind, states that in 1780 or thereabouts, Dr Charles Irving when on the Spanish Main—a term often wrongly applied to the Caribbean Sea—invented an improved method of obtaining fresh water by distillation of sea water and received a reward of £5000 from Parliament for it. Perhaps the reward was for the *improved* method, though Moseley does not specify in what the improvement consisted. Incidentally, it was this same Dr Irving who treated intermittent fever with 'London Bottled Porter' [he must have been a popular physician], stating that "nothing is so grateful to the stomach especially if infusion of snake root or cinnamon is added" and bark taken cautiously.

Lind's purification by sand filtration in a cylinder within a barrel has already been referred to. Nowadays, fresh water is taken on in ports and stored in tanks.

We have spoken earlier of the *food* on board ship in the rough times of the seventeenth and eighteenth centuries and more will

be said when we speak of scurvy and the avitaminoses. At the present day the Board of Trade regulations are strict as to standards and kinds of food, and for thorough inspection of food supplies, nevertheless, it is impossible in most cases among seamen to avoid monotony of diet, excess of salt or preserved meat, a deficiency of vegetables, especially fresh vegetables, and the food ingredients are often ill-balanced.

We have seen how in former days sickness was the lot of all seamen, how rough and ready was his treatment, how, if he failed to recover speedily, he was discharged to beg his way through life an invalid.

In more recent times there was a Seamen's Hospital, a warship anchored in the Thames. From the last of these hulks the hospital was transferred to shore and the first Dreadnought Hospital began its work at Greenwich, with a branch hospital at the Albert Dock. Advantage was taken of the increasing numbers attending there to found the London School of Tropical Medicine, largely through the efforts of Sir Patrick Manson. This later, owing mainly to the Great War, was found inadequate both for accommodation of patients and for facilities for teaching purposes and the Hospital for Tropical Diseases was opened at Endsleigh Gardens. The London School of Tropical Medicine was housed in the same building until it was amalgamated with the London School of Hygiene in the buildings now situated in Keppel Street and Gower Street in 1926.

In conclusion, let us see the stage at which we have arrived in luxuriousness of crew accommodation on vessels at the present day, bearing in mind that of 150 years ago. In vessels of Class A (the account refers, I believe, to Soviet ships, I do not think British ships have yet attained quite this level) the crew is housed in four-berth cabins, each man being provided with a full-length wardrobe and locker constructed of polished wood. Other furnishings of the cabins are a small table and chairs of comfortable design matching the wardrobe. Bunks and scuttles are fitted with curtains. To maintain cleanliness of quarters the crew change from their working clothes, bath and resume other clothing before entering their cabins. For bathing there are shower-baths, with a constant supply of hot water electrically heated and thermometrically controlled. The messroom is served through hatches and the lavatory is provided with pans of the wash-down pedestal type.

It calls for no little effort to let the mind hark back to the days

when the men worked in rags, unbathed except by exposure to the waves where the man who washed voluntarily was regarded as effeminate, when lavatory accommodation was non-existent, when he snatched his inadequate meals in his short time off watch, in damp, ill-lighted, unventilated quarters Time only will prove whether the swing of the pendulum from extreme hardship to film-stair luxury will result in producing as good, as brave, as bold, as intrepid sailors as those who built up the fame of the British Navy and Mercantile Marine

CHAPTER II

THE ARMY

In attempting to describe the conditions under which the soldier lived and moved and had his being in the eighteenth and nineteenth centuries we are handicapped to some degree by the limitations of our subject to the tropics and warm climates. Much that was written in those days was descriptive of the ordinary surroundings and circumstances of military life and expeditions were more often made to the Continent, *e.g.* the Walcheren Expedition with its disastrous termination. On other occasions, too, lack of knowledge or its application has led to disaster. More often it was the latter, want of foresight, of application of what was already known, for works of practical importance to military hygiene appeared in the eighteenth century showing that camp sanitation was no new subject. Mention must be made of Sir John Pringle's *Observations on the Diseases of the Army*, published first in 1752, of Munro's *Means of Preserving the Health of Soldiers*, which was published in 1780 and deals more with the hygiene and sanitary than the strictly medical aspect of the subject. He it was who wrote very practically on camp sanitation, on privies and pit latrines, on purification of water, on precautionary measures against typhus and relapsing fever, citing Moses and the Levitical precepts, starting a fashion which is not uncommonly followed even to-day.

In non-medical matters most men over, say, 45 years of age are apt to be *laudatores temporis acti*, but in medical matters there is too great a tendency to decry and belittle the work of our grandfathers. The health of the soldier was not neglected, as the writings of Bell, Hunter, Moseley and others clearly show when dealing with expeditions in the West Indies. It was not the medical officer that merited the blame for disaster when it occurred, so much as the carelessness, neglect and want of thought in high places.

Much of what Pringle wrote is applicable to conditions in warm climates, though his experience was chiefly gained in Flanders



SIR JOHN PRINGLE
1707—1783



EDMUND ALEXANDER PARKES
1819—1876



ROBERT JACKSON
1750—1827

and his recommendations are thoroughly practical. He describes how disease may be conveyed by putrid air, from overcrowding in camps, in barracks and in hospitals, how 'rheumatisms and consumptions' develop from neglected colds brought about by the change from a landlord's fireside to cold barracks and exposure to the Netherlands winter without additional clothing. By air from the 'corrupted water of marshes,' by allowing excreta to lie about the camp dysentery may be set up, as it may also from the custom of leaving straw to stay rotting in the tents. His suggested remedies are quite logical. Frequent change of camp and of straw which was the customary bedding, fixing camp sites away from marshes or fields lately flooded. In the dysentery season, he says, some slight penalty should be rigorously inflicted on every man that shall ease himself anywhere about the camp except in the privies. Apparently in non-dysentery seasons he found no objection to such a procedure. He preferred barns to houses for billeting because the likelihood of overcrowding was less. The hospitals of the day left much to be desired. Ventilation was bad, overcrowding the rule, infection often acquired there, and the medical officers were terribly overworked. It was quite the usual thing for one medical man to be in charge of 700 beds.

Errors in the soldiers' diet were another common cause of sickness. Pringle noted how that the food-supply was better regulated when the men were joined in messes, the individual's pay was so small that there was no chance of excess in eating. He had no belief in fruit as a vehicle of dysentery for, he argues, autumnal fever and dysentery are either "of an inflammatory or putrid nature and cannot be owing to what is acid." Soldiers are not fond of fruit, he adds, nor have they the means to purchase it. A few disorderly soldiers rob orchards, but the most regular are equally subject to fever and dysentery. He mentions the value of what he calls 'under waistcoats,' we now speak of them as cholera belts, which even to-day few *habitués* of the tropics would be without. "Some of the officers who had been subject to return of the flux," he says, "have informed me that they found much benefit from wearing a flannel waistcoat next their skin." None of the foreign soldiers were without them. He considered the provision of blankets for soldiers but doubted whether the expense and impediment of so much more baggage would not overbalance the advantage. It is good to note that after the earlier editions of Pringle's book were published foot-soldiers when on service were given blankets.

His account of the prevalent diseases of his day in the Army is interesting clinically and it is an intriguing study to work out the diagnoses by the help of modern knowledge. The former comes within our province, the latter does not. Vernal intermittents, either tertian or quartan, were rare, he found, except in those who had had the fever in the preceding autumn. The significance of this will be seen in the study of malaria. In the hot season marsh fever was apt to run into double paroxysms, in other words was subtertian or æstivo-autumnal fever. Helminthiasis among the troops was very common, especially the round worm, by which there is little doubt he means *Ascaris*, which was often passed in the stools and sometimes ejected by vomiting. With our knowledge of the life-history of this parasite we may infer that rats must have been common in the camps and billets. Jaundice, again, was frequent, and was very likely due to the same vector, rats infected with *Leptospira icterohæmorrhagiae* [we may again remark that Pringle's experience was largely acquired in Holland where water rats would be common from the system of dykes]. He speaks in some detail of an intermittent or remittent fever lasting for about three weeks without any sensible fall in temperature, which would probably be typhoid fever, and also of a fever lasting for 14–20 days with, at times, petechial spots or blotches, which was almost certainly typhus, especially as he states in one place that they were very like cases of jail or hospital fever and notes particularly that they differ from fevers of the West Indies "where there are intermitting and remitting fevers with bilious vomiting and later black vomit. Moreover, the latter attacks newcomers, whereas the former attacks natives as well as strangers." He is clearly referring to yellow fever, though there seems to be no reason for confusing yellow fever with either enteric or typhus fever on clinical grounds. He tried quinine but, as would be expected, found it useless "till convalescence when it was good as a strengthener, whereas in the tertian or quartan form of fever it was a sure remedy."

The camp dysentery described by Pringle was clearly, from his account of the clinical symptoms, the character of the stools, the fever and the post-mortem appearances, the bacillary form. He ascribes the infection to "foul air, bad diet, and nastiness," a comprehensive, expressive term, but lacking definition. He quotes Degner as giving good reasons for its being due (at Nimeguen, for example) to personal infection from one to another of those occupying the same tent and from that to the next.

The foul straw becomes infectious, but the greatest sources are the privies after they have received the excrements of those who first sicken. The hospitals likewise spread it, since those who are admitted with the flux not only give it to the rest of the patients but to the nurses and other attendants of the sick.

It is strange that he makes no mention of flies which must have been a pest in these camps. How near he came to the truth is seen from a later statement when he says that "having perused a curious dissertation published by Linnæus in favour of Kircher's system of contagion by *animalcula*" he suspended his decision as to hypothetical causes till this had been further investigated.

We thought in the South African War that we had hit upon a new discovery when we obtained good results with concentrated salines in this form of dysentery, but Pringle refers to a method of treatment successful in the hands of an army physician, a Dr Huck, who had seen service in North America and the West Indies. This consisted in giving Glauber's salt in solution every half-hour till two or three copious stools resulted.

Some of the cases described as dysentery contracted in hospital were probably not dysentery at all, but the result of irritant poisoning, possibly copper acetate or subacetate. He says that the dysenteric symptoms may be kept up or even initiated by the hospital kettles 'made of copper tinned'.

The tinning soon wears off, the metal is corroded by every liquid that is salt or acid, and we may well imagine how apt the nurses will be to let such things stand in those vessels and to neglect cleaning them before they are again used.

[A contrast to modern times when the Royal Army Medical Corps repeatedly wins the prize for cookery.]

I suspect [he continues] that this may be often the cause of mischief, especially during the dysenteric season, when the stomach and bowels are otherwise so much disposed to be out of order. It would therefore be an advantage to military hospitals to have a Brazier [*i.e.* a tinsmith] constantly attending them.

He has a good deal to say about jail or hospital fever which he appears to confuse with enteric and cerebrospinal fevers. It occurs not only in hospital and jails, but in crowded barracks, transport ships and in any place ill-aired, kept dirty and filled with "animal steams from foul or diseased bodies." The rash is one apparently first described by Frascatorius as lenticular, puncticular, or peticular and in an appendix he explains his interpretation of petechiæ as small spots which when confluent become blotches like a measles rash and are not the same as flea-bites.

This would seem to be in part enteric fever with its lenticular spots, and he describes graphically the typhoid state, but some cases, he notes, end in crisis before seventeen days, these are almost certainly typhus. Others go for twenty days or more without crisis and the eruption may be so little conspicuous that it is not seen unless carefully looked for, this is surely typhoid fever. That some were cerebrospinal fever we may justifiably infer from the fact that they were cases of 'spotted fever' and that at post mortem "a most unexpected appearance found was about 3 oz of purulent matter in the cerebral ventricles and at the upper part of the cerebellum, while others who had been ill for about the same length of time had no abscess."

Among malignant fevers he mentions the crew of a French ship at Nevis, West Indies, who had killed some cattle on the island and soon afterwards were seized with pain in head and loins, great weakness, disorder of the stomach, and fever, some had carbuncles and some died. They had evidently eaten a carcase infected with anthrax, and some had acquired infection from soiled hands, possibly from the hide. We see similar cases to-day among natives who dig up and eat the meat of an animal buried after dying of anthrax.

He ascribes these fevers, excepting perhaps the last, to marshes, to putrefaction of animal and vegetable substances, to low-lying and ill-aired populous cities unprovided with common sewers, where the streets are narrow and foul, houses small and dirty, fresh water scarce, jails and hospitals crowded, not ventilated nor kept clean, slaughter houses within the walls, dead animals and offal left to rot, drains not carrying off stagnant water, grain old and mouldy, food deficient and so on, "in short, the same as cause plague." This seems to be rather an enumeration of all the insanitary conditions he had witnessed grouped together as a conglomeration of possible causes than a scientific account of the ætiology of the fever or fevers he has just been describing. The fatality due to jail fever was well known from the historical outbreak associated with the Oxford Assizes in 1577 referred to by Lord Bacon, and in Pringle's day at the Old Bailey in 1750 when a hundred prisoners were kept in two rooms opening into the court, each $14 \times 11 \times 7$ feet, and four of the six judges died, two or three of the counsel, an under-sheriff and several of the jury—forty in all, not counting those of lower rank and spectators whose deaths may not have been heard of or at least not connected with infection contracted at the trials.

Of minor diseases communicated by direct contact, or by

clothes, bedding, etc., it was very common among soldiers in barracks or on ships. Pringle goes so far as to say "an army cannot be entirely freed from the itch."

A close follower, almost a contemporary, of Pringle was Robert Jackson (1750–1827), who practised in Jamaica and served with the Army in America, the West Indies and in Flanders. He wrote a work on the fevers of the West Indies, in particular Jamaica, and also observations on preservation of the health of soldiers in warm climates. He had no scruples about opposing Pringle's ideas if he thought them wrong, nor of coming into conflict with those high in authority regarding the organization of the Army Medical Department. Many of the points for which he strove came to be adopted later, after the disastrous failure of the Walcheren expedition in 1809 when nearly 30,000 officers and men were attacked by fever with a mortality of 346.9 per thousand. The conduct of affairs was taken out of the hands of a triumvirate composed of a Surgeon-General, a Physician-General and an Inspector-General of Hospitals, and put in charge of a Director-General with three chief assistants. Under the former régime within a few years 90,000 British troops had died, nearly all from disease due largely to ignorance and neglect, in the West Indies. The first Director-General was an able man Dr James McGrigor (later Sir James) who had seen service in Walcheren, the East and West Indies, Egypt and the Peninsula, as well as at home.

Hospital arrangements in the British Army at the end of the eighteenth century were very defective and changes were made, to say the least, arbitrarily. Without actually mentioning names we may give the following quotation of a recorded complaint in 1794:

Experienced regimental surgeons have been put aside by order of an old broken-down court physician of London—an apothecary from Weymouth, chosen by George III to direct and administer the complicated and difficult medical and sanitary affairs of immense armies, constantly engaged in active warfare, in various countries. He purposely superseded men like Robert Jackson and placed over them graduates of English Universities.

This is, we feel sure, meant to be very cutting.

It is not right to restrict our remarks to British military medical officers and to omit men of outstanding merit belonging to other countries. René Desgenettes, Napoleon's Principal Medical Officer, was an energetic sanitarian with views in advance of most medical opinions of his day. When on the Egyptian campaign he made it his chief duty to protect the Army against the introduction of

disease from without His arrangements would bring no discredit on a military medical officer of to-day He instituted a special sanitary organization to watch the ports, he established bureaux of hygiene in different parts of the country to keep him informed of the prevalence or existence of disease in the various districts In spite of all his efforts, however, plague broke out and to combat it Desgenettes transformed a large mosque at Alexandria into a hospital for observation of suspects and organized two special hospitals for those definitely infected He put into segregation half a brigade of infantry among which a large number of cases had occurred

A force of 15,000 men free from plague was sent to Syria, Napoleon himself being in command and Desgenettes accompanying him At Jaffa plague broke out and cases became so numerous that first one and later a second hospital were needed Desgenettes had a lucky escape from results of what can be described as a piece of bravado and a foolhardy thing at that To hearten the men Napoleon would visit the hospitals and converse with the patients, and Desgenettes *pour encourager les autres* dipped his lancet into a suppurating bubo and therewith pricked himself in the groin and axilla He suffered merely from a local inflammatory lesion, we know now that, fortunately for him, a suppurated bubo contains as a rule few or no plague bacilli It is said that the gesture had a most heartening effect on the troops, so it served its purpose

Returning to Cairo, Desgenettes set up a *Commission extraordinaire* of public health, giving it authority to issue any order it might deem necessary, subject only to the approval of the Commander-in-Chief He divided the country into areas, each with its Public Health Committee to deal with local matters, but reporting to and acting more or less under the direction of a central body Since the cause of plague was not known for nearly a century afterwards and the mode of infection later still, success in preventing extension of the disease could not be expected and plague persisted in spite of prompt notification and rigorous isolation of patients

The soldiers' worst enemy, the greatest obstacle to the success of a campaign has at all times been disease, not bullets To give but a single instance of a thousand deaths in the hospital at Scutari, 575, or more than half, were due to dysentery and diarrhoea, 173 to fever, and only 53 to wounds These figures are exclusive of those dying within a fortnight of admission

For many years prior to this, British medical officers, both naval and military, had been trying to establish principles in prevention of disease, and the labours of Pringle, Lind, Blane, Jackson, Trotter and Henry Marshall, to name but a few, did much to found the science of medical statistics. As regards India, particular mention must be made of Sir James Ranald Martin, who in 1835 submitted to the Government of India a detailed plan of a system by which all medical officers were required to send in reports on the Medical Topography and Sanitary Statistics of the districts, stations and cantonments under their care. Dr Farr of the Registrar-General's Office speaks of these in terms of high praise. We may note in passing the use of the term 'Medical Topographer' as applied to one who investigates "circumstances tending to deteriorate the race, the external causes of disease, and the propagation and prevention" of them. Dr Farr himself stated "In the science of health there are more exact and demonstrable truths than in the science of disease and the advantages of prevention over cure require no proof."

There has, at all events up to the present century, always been an unwillingness on the part of combatants, even commanders, to accept or learn from medical officers what they could not be expected to know of themselves. Many a time and oft commanders have, without any first-hand knowledge and without attempting to consult the medical officers, issued orders regarding the soldiers' health, with results frequently disastrous. It was in truth a woman, Florence Nightingale, who said

The observance of sanitary laws should be as much part of the future regime of India as the holding of military positions or as civil government itself. It would be a noble beginning of the new order of things to use hygiene as the handmaid of civilization.

This seems to be a truism now, but when she spoke these words, it was a revolutionary innovation.

There can be no glossing over the fact that a century and a half ago the hospitals themselves were one of the chief causes of sickness and mortality in the Army. (We have noted the same previously as regards seamen.) It had been noticed that among the infantry who were taken into hospital for treatment the death-rate was heavy, whereas the cavalry carried their own sick and they were treated regimentally and among them the mortality was slight in comparison, for contagion was fostered by what were called the "accumulated horrors of hospital miasm." Dr Knox, at a later date, wrote that "the mortality in hospitals

after battles is so terrible to behold that I feel convinced it would be preferable to tend the wounded in the open field " ¹

We have mentioned that in 1835 Sir Ranald Martin suggested the appointment of a Medical Topographer. He was to be attached to the Quartermaster-General's department and in time of peace his duties were to include selection and inspection of sites of camps and cantonments, reporting upon the condition of barracks, hospitals and transport ships, while in time of war he accompanied the Quartermaster-General in the field and, where military reasons did not hold the place of paramount importance, his opinion was to be obtained regarding sites for encampment and other matters of sanitary importance. Had this principle been in force the Walcheren expedition would never have been allowed to encamp in a pestilential site, nor the Guadiana expedition the following year.

The soldier—the man of the rank and file—was far from being the hard-drinking, careless, reckless libertine that some of the works of the nineteenth century (more those of fiction than of fact, it is true) would have us believe. Florence Nightingale, whose experience of them under the rough and hard times of the Crimean War (1854) was extensive, wrote:

I have never been able to join in the popular cry about the recklessness, sensuality and helplessness of the soldier. I have never seen so teachable and helpful a class as the army generally. Give them schools and teachers and they will come to them. Give them books and games and amusements and they will leave off drinking. Give them work and they will do it. Give them suffering and they will bear it. I am struck with the soldier's superiority as a moral and even [*sic*] as an intellectual being.

Martin's advice and suggestions on the Hygiene of Camps and Cantonments and his Sketch of Medical Arrangements for Field Service and Sanitary Precautions necessary in Camps, Barracks and Hospitals are very sound and might well be, in fact most of them are, followed even to-day.

It was Frederick of Prussia who stated that fevers cost him as many men as seven battles and Martin wrote

¹ If I may be pardoned a personal reference, I can fully endorse this from my own experience in the South African War. Those who were wounded, we noticed this particularly in pulmonary and abdominal wounds, and brought into hospital quickly and operated upon had a high mortality, even with the best surgeons available. Others who could not be found for twelve hours or more, owing to the growing dusk or being still in the line of fire, showed a far lower fatality—the air was pure and they could not obtain food, there was no harmful 'miasm'.

Where the hygiene of an army is judiciously regulated, the soldier may be kept in health and vigour, but allow an ignorant general to encamp on a marsh, let filth stagnate, fatigue excessively the men, crowd them in low damp rooms and, despite of drugs, they will fall as unripe and blasted fruit, not by the sword but by the fever

It had been his experience, as likewise that of his predecessors and others after him, that unwholesome stations and unsuitable encampments rendered courage useless and enterprise impracticable, destroyed the personnel of fleets and brought about the melting away of armies. The attack on Cartagena is yet remembered when

the Spaniards from their ramparts saw their invaders destroyed by the hostility of the elements, poisoned by the air, crippled by the dews, when every hour swept away battalions and in the three days that passed between the descent and re-embarkation half an army perished

Only a little less tragic were the expeditions to Walcheren, Aracan and Rangoon. The first of these was probably the largest expedition ever launched up to that time (1809), comprising 70,000 sailors and soldiers. They set out at the most unhealthy time of the year, the summer. Previous experience, when a Scottish regiment in the Dutch service had been known to lose their whole numbers in three years, was ignored, it was known that the French Army annually lost one-third of its complement there, and a Dutch corps, which on arrival in 1806 was 800 strong, by 1809 had become reduced to eighty-five. Some fifty years before, in 1754, Sir John Pringle had described the climate and its diseases. The force landed on the last day of July and the first of August and by the 10th October 587 per thousand had fallen sick and 142 per thousand had died. Ten thousand lives were lost through the ignorance—in these days it would almost come under the head of criminal negligence—of those in authority

M. Budin, in his interesting work *Statistics of the Sanitary Condition and Mortality of Forces, by Land and Sea, as influenced by Season, Localities, Age, Race and National Characters*, gives examples of the losses of armies from disease, showing how they exceed greatly in time of war those caused by death or wounds in action. The Walcheren expedition which he quotes we have just now mentioned. In the Rangoon expedition of 1824–5 deaths from wounds were thirty-five, by disease 450 per mille. In the Burma expedition the following year, the enterprise in Aracan was speedily brought almost to naught by the malignant fever of the country. Of European and native soldiers 5500 were struck down early (camp-followers are not included in this figure)

and soon "everyone who was not dead was in hospital" Of the original European force three-fourths died, and it was said that the miserable residue were ruined in constitution and did not survive for long

Brief reference may be made to the disasters and heavy mortality which befell military expeditions to warm climates in those days Thus the British force of 10,000 sent to San Domingo was reduced to 1100, a loss of 89 per cent, without a blow being struck or the enemy being sighted

In Jamaica in the first fifteen years of the nineteenth century, and probably earlier, but of that we have no accessible records, soldiers died at the rate of 130 per mille Then Lord Metcalfe, a layman in medical matters but with opinions in advance of many of the medical authorities of his day, brought forward a measure for erecting barracks on the hills, probably what is now Newcastle, where the troops still go for the hot summer months, and after 1842 the mortality was reduced to thirty-five per mille, or by more than 75 per cent The observation has been made that Maroon Town, 2000 feet above sea-level, did not suffer from the deadly fevers of the low-lying and coastal parts of Jamaica, and even against the yellow fever a rise of 2500 feet had been found to be a sufficient protection

It was at Lord Metcalfe's wish that Sir Ranald Martin prepared a scheme for new barracks and hospital accommodation This scheme was found suitable not only for the West but also for the East Indies, and for Gibraltar, Malta, the Cape, Mauritius, Ceylon, China and Australia, and "easily adaptable for other Colonies"

Turning from the West to the East we find Inspector-General Macleod reporting that for thirteen years at Berhampore, Madras, the average annual admissions into hospital amounted to 2196 per thousand and deaths averaged 106 per thousand, the chief causes being fever and dysentery Formerly the bane of the Army had been 'famine and ague,' now it was 'scorbutic dysentery'

One author writes pithily on the effect of the climate of India on the army there

For the first twenty years of military service increased age may be some indication of increased efficiency, but after that period this congruity gradually ceases till every year that is added to the age of the officer detracts from his utility, and seniority declares him fit for the highest command just when the inexorable hand of time has stripped him of his last qualification for any

Sir Andrew Halliday, Deputy Inspector-General of Army Hospitals, wrote in 1839 a long instructive and informative letter to the then Secretary at War on Sickness and Mortality among Troops stationed in the West Indies. The reason for the letter was a matter to which most medical officers in the services, Naval, Military, Colonial (the author has no first-hand knowledge of the youngest, the Air Force), have been at one time or other subjected—a report on medical matters by a layman. The communication of Sir Andrew Halliday deals with a review of a report called for by those in authority from a Captain Tulloch. He begins by lamenting that a layman should have been asked by responsible officials to furnish a report on medical and professional questions, but at the same time he knows that “this is not a new departure, that the medical officer is always despised and disregarded.” Thus, at Barbados, Halliday’s predecessor as Deputy Inspector-General of Hospitals had made many recommendations for cleanliness and for the greater comfort of the troops, but so little attention had been paid to his suggestions that the soldiers preferred to sleep on bare boards in the open galleries (passages or verandahs) or “were forced to the grog-shop to escape the myriads of bugs and vermin that were hatched in the stuffing of his palliass, and brought forth in swarms ready to devour his body.” These palliasses, it may be said, were stuffed with crude husks of the Indian corn and must have been far from comfortable even without the vermin.

Halliday goes on to criticize the injudicious manner in which medical officers and troops are selected for the West Indies. The youngest medical men and the most recently joined recruits, he says, are sent there as their first station and the former—the medical officers—acquire all their experience in tropical disease from their mistakes in treating the latter, the new recruits. He gives examples of bad choice for the locality of barracks and of the poor accommodation. At Tobago in 1827 which, he says, is one of the best in the West India command, the hammock-space allowance was only 22–3 inches per man. The barracks were situated on the lee-side of an extensive swamp and “the garrison here is always decimated and often nearly annihilated.” Among West Indian troops every soldier is under medical treatment for one disease or another once every six and a half months and between eighty and eighty-five per thousand annually during the twenty years 1814–34 have died, or about one-eleventh of the military force. Taking all classes of fever together the medical returns show that one out of every twenty admitted to hospital

died, in some classes of fever 1 in 9 and in that denominated 'icteroedës' as many as 1 in $2\frac{1}{2}$. Halliday adds "In the only instance in which I had an opportunity of witnessing this aggravated form of bilious remittent, one only of five patients seized escaped" It is not improbable that the infection was not malarial bilious remittent but yellow fever, the two were not infrequently confused (see later)

Next to fever, gastro-intestinal affections were the most common, ascribed to the "careless, uncomfortable and crowded manner in which regiments or detachments have generally been conveyed from one colony to another" Men, women and children were all huddled together on deck, often there was barely standing-room and they might be kept thus for one or two days and nights Unless the journey was a short one, such as from Barbados to Grenada or St Vincent, the voyage would certainly not be accomplished in less Thus crowded they would be exposed to the night and morning chills and dew, and possibly deluging rain, alternately with the scorching, burning rays of the sun and in a state of wretchedness and filth reminiscent of the slave days, except that the slaves were between decks, a state which beggars description, for they could not observe the common decencies He adds

However healthy they may have been when they embarked, it generally happens, if the voyage has been at all lengthened, that many land already labouring under acute dysentery or inflammation of the lungs, and that more are seized with these complaints immediately after their arrival, or with the colony fever to which the previous exhaustion has rendered them peculiarly obnoxious

No regiment, he maintained, should be allowed to remain longer than two years in any one colony, Jamaica he thought more unhealthy than most (British Guiana excepted), and the troops there ought to change their quarters annually For many years after British Guiana came into our possession (in 1831 British Guiana was constituted out of Berbice, Demerara and Essequibo) it was not only considered but actually must have been the most unhealthy of all the British colonies Few men survived a three years' residence on its muddy shores and Demerara was emphatically termed 'the wet grave of Europeans' (but see also p 86)

The wretched barracks of the time were not only inadequate in space for the number of occupants, but were so closely shut by night that the air must have become almost unbreathable The so-called windows, which were merely open holes by day, were covered with wooden shutters which excluded wind and rain while

designed to keep out the miasma or marsh air and were emphatically and aptly designated by the men as 'the suffocators'. Between 1821 and 1828 the white troops stationed there numbered 6639 and of these 764, or 11.5 per cent, died. Thereafter new barracks were built, 'suffocators' were abolished, and among 8016 troops quartered in them the report states that only (mark the 'only') 489 or 6.1 per cent died. That is, the mortality rate was reduced nearly to half, in these days even this rate would be considered as very high.

From his observations on British Guiana Halliday seems to have had a hazy idea of the possible connection of mosquitoes with malaria, or perhaps we ought to put it somewhat more vaguely, as a connection between insects and disease. He writes

The clouds of sandflies that stretch along the shores of British Guiana, though individually scarcely perceptible, are so blood-thirsty and annoying as to surpass even the mosquito, and are, I would say, a link in the chain which may connect the dragonfly (also an insect of the water) with the invisible but not less active insect that constitutes the *marsh miasmata*. These insects cannot live in so low a temperature as that which is found within the tropics at an elevation of 2500 feet above sea level and we know that even in England when the temperature of the air rises above a certain point, fever and ague were and are always generated in our fenny countries.

Fevers in Trinidad and Tobago, Halliday remarks, have generally assumed a most malignant type. Between mid-February and 8th July, 1820, of a detachment consisting of 6 officers and 123 non-commissioned officers and privates, 11 women and 6 children, 146 in all, 138 were attacked with fever and 100 died, i.e. a morbidity rate of 94.5 per cent, a mortality rate of 68.4 and a fatality rate of 72.4 per cent.

At Barbados, to the insanitary state of whose barracks we have referred above, bowel complaints seem to have been the most fatal. Here, men, women and children were all compelled to use the same open and foul privies, and vermin, it is said, were generated in millions. These privies were situated far from the barracks themselves and when the occupants had to visit them at night they were compelled to go from their beds in a state of profuse perspiration, and if the weather was inclement often would return so drenched with rain and chilled that they would be down in a day or two with acute diarrhoea or dysentery, or pneumonia. The result naturally was that the death rate was high and many who survived became totally unfit for service and had to be sent home invalided to die of lingering consumption or chronic hepatitis.

It was not so much the climate as the locality of the barracks and quarters that was the cause of ill-health among the troops. The new arrivals were often, we might say usually, sent to the worst stations in the command and might be kept there till half or even two-thirds of the whole corps had perished. Halliday suggests, though he seems to have had small hope of his suggestion being accepted, that new arrivals should be sent for their first year to one of the more healthy stations till they had become more inured to the climate and the ways of living in a new colony.

It was the custom for sergeants (this was told to Sir Andrew Halliday by one of them and appears to have been accepted in all good faith by him) after the fatigues of the day, when the hour arrived for going to bed, to take a large dose of strong rum, which they called 'putting on their night-cap'. If, on account of special duties, they had to forgo this, to them, invigorating draught for two or three nights in succession they became so debilitated that they were either carried off by delirium tremens or fell victims to the first attack of fever.

Edmund Parkes, one of the most famous of sanitarians, at one time Professor of Hygiene at the Army Medical School, reduced the incidence of tuberculosis and other respiratory diseases by procuring more floor space and air space in barracks. When General von Moltke heard of the death of Parkes he is reported to have said that every regiment in Europe ought to parade on the day of his funeral and present arms in honour of one of the greatest friends a soldier ever had.

We may briefly sum up matters by saying that down to the time of Parkes the chief aim of those who planned barracks seems to have been to place as many men as was possible on the ground at disposal, regardless of site, ventilation, orientation for sunshine, direction of prevailing winds and so on. We may cite as examples of the time in the United Kingdom the Hulme Cavalry Barracks at Manchester, or the Linen Hall Barracks, Dublin, almost any colonial barracks exhibited one or more of these defects. It is not to be wondered at, therefore, that barracks themselves were a fertile source of illness—from without by bad situations, from within by infection from overcrowding, lack of cleanliness and sepsis. Barracks were so concentrated that there was every impediment to the free circulation of air, even had the surrounding air been healthy, and abroad they were situated at the edge, sometimes, as we have seen, on the lee side of a swamp. It was common for the beds to be placed in long lines, almost touching one

another, the room being lighted and ventilated from one end only

In the latter part of the nineteenth century, largely as the result of Parkes's efforts, there came a great change. The whole structure was made more airy, each man was allotted more space, the buildings were smaller so that there might not be too many men herded together, beds were arranged differently and instead of long rows side by side, almost in contact, there was one in each corner, the others in pairs between windows. In the tropics and subtropics further protection was obtained by having thicker walls, wide verandahs, more man-space, while gauze was employed to exclude flies entering by doors or windows from the cook-houses.

The older types of *married quarters* consisted of single rooms, two on each side of a central stairway, on two or three floors. An improvement on this was the 'three-room quarter'—a living-room, a bedroom and a scullery. Later came quarters with differing numbers of rooms and in style of finish *according to rank*, not family needs, and domestic conveniences were separate from the living-rooms. These in turn were replaced by a verandah type of dwelling with conveniences at the end of the block, the quarters being allotted, not as before according to rank, but according to the size of the family.

We cannot here trace in detail the changes in equipment designed for the better hygiene of the soldier, and the disposal of it for body-carriage, nor the changes in clothing which have been made from time to time according to the exigences of the climates in which the soldier may be called upon to serve. Much attention has also been given in recent years to what may be called hygiene of the march—the length of march, the best time of day and the speed—and the siting of camps, the water-supply, purification of a dubious water and so on. Consideration of these matters in detail would carry us too far into the minutiae of military administration. The benefits derived from them are well seen by a comparison of the returns in the beginning of the second half of the nineteenth century with those early in the twentieth. In 1859 admissions for sickness in the British Army, all troops, at home and abroad, were 1120 per mille, in 1906 they were 592.9. The death rates were 18.2 and 5.5 respectively and the invaliding rates 16.0 and 11.9. The following figures from Notter and Firth's work (they are home returns, those for the tropics are not so good) show that about the middle of the nineteenth century the mortality rates among civilians were about half those of soldiers at the corresponding ages, whereas half a century later

the ratio was practically reversed, the mortality among soldiers being considerably the lower

Year	Ages in Years							
	20-25		25-30		30-35		35-40	
	C	S	C	S	C	S	C	S
1855	8 4	17 0	9 2	18 3	10 2	18 4	11 6	19 3
1906	5 1	2 6	6 3	2 7	6 8	5 8	11 1	8 5

During war the principles of hygiene cannot always be applied as fully as those responsible for the soldiers' health and well-being would desire, so much must depend on service needs and administrative possibilities. It is a well-known fact that in all wars, till the Great 'World War,' deaths from disease far outnumber those from wounds. The following table (from Notter and Firth) demonstrates this very clearly, the figures being given to the nearest integer per thousand strength.

Campaign	Admissions		Deaths	
	Disease	Wounds	Disease	Wounds
Ashanti, 1873-4	474	70	16	6
Zululand, 1879-80	739	12	25	2
Afghanistan, 1879-80	870	51	36	7
Egypt, 1882	554	29	6	7
Sudan, 1885-6	1100	47	29	10
Ashanti, 1895-6	49	—	0 5	—
Chitral, 1895	1530	14	49	5
Nile, 1898	1101	57	36	16
South Africa, 1899-1901	746	34	69	42

For comparison we may mention, though the campaigns and expeditions were continental and not tropical, that at Walcheren in 1809 the mortality from disease was 347 per mille as contrasted with 16 7 killed by the enemy, in the Peninsular War deaths from disease were thrice those dying from wounds or killed in action, and the sickness rate was so high that during the year more than twice the whole army were the numbers admitted to hospital. Lastly, in the Crimea (1854) deaths from disease were 230, from wounds or in action 150 per mille.

The following are important dates in Army Medical Adminis-

tration In 1748 there were three types of army hospital—flying, fixed and convalescent The wounded received treatment from regimental surgeons at the front, and they were then collected at ambulance stations, to which came also those who were able to walk and there capital operations were undertaken As soon as they could be moved from these the patients were transferred to one or other of the general hospitals in the nearest city, or, when these became overcrowded, to similar hospitals farther back It was not till 1762 that army hospitals were placed under military regulation and another quarter of a century had passed before there was a regular medical examination of recruits and government barracks took the place of billeting

Munro, who wrote as long ago as 1780, had remarkably clear ideas, in fact ahead of his day, on military sanitation On several matters his views are strikingly modern, such as those on the disposal of refuse and excreta, purification of water, camp sanitation, prevention of typhus and relapsing fever

Coming to more recent times, to what may be called the sequelæ of the Crimean War Though the name of Florence Nightingale is held in high repute, largely by reason of her nursing and hospital work, probably more widespread and permanent benefit arose out of her *Observations on the Sanitary Conditions of the British Army in India*, 1863 It was owing to her that Sidney Herbert appointed a Commission for the consideration of Military Hygiene in an unrestricted sense As a result an Advisory Board in Military Hygiene was constituted and an Army Medical School established at Netley

Passing mention only is made here of Bruce's discovery of the causative organism of undulant fever, or as it was then named Malta Fever, the *Micrococcus melitensis*, now relegated to the group *Brucella*, so named in honour of Sir David Bruce It is not that this discovery was not a great one and far-reaching in its results, for the remedial and preventive measures are so simple that the Mediterranean station has thereby been robbed of its chief terror (see Chapter XIII, Undulant Fever)

The South African War of 1899–1902 taught a salutary, though bitter, lesson, driving home how poor was sanitary organization in the field under conditions of active service Apart from the medical personnel, neither officers nor men had knowledge of preventive measures and there was little if any co-ordination between the medical and the combatant branches of the Army, in short, this war may be regarded as practically the beginning of the scientific study of disease in the field

Sir Almroth Wright's antityphoid vaccine, which he had tested during the preceding two years at Barming Heath Asylum, had yielded good results, though better were to come later when the paratyphoid fevers were differentiated from typhoid and a mixed enterica group vaccine was prepared which gave more extensive protection than the *Bacterium typhosum* vaccine alone could accomplish. Its use, however, at that time was still in the experimental stage, the method of preparation was not perfect, nor was the dosage fixed. The records of the war showed that 57,684 cases of enteric fever occurred and that 8022 died of it—more, that is, from this disease alone than were killed in action. Dysentery, long regarded as the scourge of armies, also took a heavy toll. Investigation of this in 1900 by a Commission of which Bruce, Notter and Simpson were members was the reason for the establishment of a laboratory at Pretoria.

After the South African War the Army Medical School was transferred from Netley to London where it came more into touch with the hospitals of the metropolis and the teaching there. Further, a School of Sanitation was started at Aldershot and—a most important, wise and far-seeing move—a course of instruction was instituted for cadets at the Staff College, Camberley, and also another in India. The fruits of these measures were seen in the Great War of 1914–18 when military hygiene attained a veritable triumph. Prophylactic inoculation against infection by one or more members of the enterica group became a routine procedure, for the first twelve months against typhoid alone. Statistics of incidence have been given in official returns comparing that among the inoculated with that among the uninoculated, and attention then became focused on the *germ carrier*. Widespread employment of tetanus antiserum saved many lives and much suffering. To convey some idea of what this advantage means let us hark back for a moment to Blane's account of a fight at sea.

In April [he says] 266 were killed outright on board, 67 died of wounds, 15 with symptoms of the locked jaw. Few recovered from tetanus and the success seemed owing more to something favourable in the man's constitution than anything peculiar in the treatment which consisted in the administration of the warm bath, opium and camphor, with mercurial friction on the jaw.

Elsewhere he remarks on the frequency with which sailors injured feet or hands with splinters on deck and how often even a slight wound would prove fatal from locked jaw. The treatment as detailed is certainly more humane than that recommended by Lewis for infants suffering from *Tetanus neonatorum*.

I had been so positively assured that the custom of plunging negro infants, immediately upon their being born, into a tub of cold water, infallibly preserved them from the danger of tetanus, that, on leaving Jamaica, I had ordered this practice to be adopted uniformly. The negro mothers, however, took a prejudice against it into their heads, and have been so obstinate in their opposition, that it was thought unadvisable to attempt the enforcing this regulation. From this and other causes I have lost several infants—(M. G. Lewis, *Journal of a West Indian Proprietor, 1815-17*)

But to return to the Great War. In no previous war were disinfection stations set up to destroy the vector of trench fever, relapsing fever and typhus. The merits of cleanliness in the field, so far as it was possible, were amply recognized and methods tending to keep down flies by dealing with excreta, human and animal, on scientific sanitary lines were zealously applied. Personal hygiene, sanitary demonstrations, mobile and stationary laboratories enabled early diagnosis to be made and prompt measures to be taken to treat the sick and prevent spread of infection.

It must not be inferred that the success of preventive and sanitary measures in the Great War implies that nothing more remains to be done. Though many lessons of the earlier wars bore good fruit, we found that certain places, certain circumstances, brought forward difficulties for which we were not prepared, while local conditions might render nugatory measures which had proved successful elsewhere.

It will not be amiss, before we close this chapter, to consider one or two of the chief diseases, to show what havoc they wrought in former wars, and contrast the results with the most recent—the South African War, the European War and the Italo-Abyssinian campaign.

In the Great War of 1914-18 one of the main causes, perhaps the greatest, that paralysed the allied advance in Macedonia was *malaria*. Some battalions had 95 per cent of their complement, officers and men, stricken with malaria within a month of leaving Salonika. In 1916 out of the Macedonian Expeditionary Force of 123,394 officers and men there were 32,018 admissions to hospital for malaria and 287 deaths. In the following year the strength of the force rose to 182,583, of these 71,412 were admitted and 228 died from malaria, in addition there were 12 deaths among 43 cases of blackwater fever. During the seven months, May to November (the Balkan malaria season), there were 60,977 admissions. In 1918, among a force of 128,747 there were 59,087 malaria admissions, 272 deaths and 133 cases of blackwater fever, 28 of them fatal.

Turning next to the East African Expeditionary Force in 1916 its strength was 58,114. Between June and December there were 50,768 admissions for malaria and 263 died from it. In 1917 the average strength was 50,702, admissions reached the enormous total of 72,141 and 499 deaths occurred from malaria.

It is instructive to compare these figures with the official returns of the Italo-Abyssinian War. Among 500,000 troops there were 1241 cases of primary malaria and 1093 admissions for relapses, only 23 deaths were reported, including those dying from blackwater fever. It must not be forgotten that the Mareb region, northern front, is a bad malarial district, as is also the whole of the southern front, where the disease is general among the indigenous Somali population. Had this Italian force been attacked in the same proportion as that of the British in German East Africa in the Great War, cases would have numbered 400,000 and deaths 2500. When possible, mosquito-nets were used and antilarval measures carried out, neither of these was always possible with troops on the move, but all were able to take fifteen grains of quinine daily.

Let us next consider *dysentery*—the scourge of armies and more fatal in former wars than bullets. Losses by the French were heavy in their wars in Algiers and Tunisia (1881), in the Tonking war, in the Madagascar expedition and in our armies during the Boer War. To come down to recent times, between April 1915 and June 1916 the British Expeditionary Force at Gallipoli comprised 4161 officers and 112,677 N C O s and men, a total of 116,838. Among them occurred 29,728 cases of dysentery and 811 ended fatally. That is, more than one-fourth of the force contracted the disease, and the figure given does not include 10,383 cases of 'diarrhoea' admitted to hospital.

In 1916 the strength of the East African Expeditionary Force was, as already stated, 58,114 between June and December. Of these 8902 were admitted on account of dysentery and 306 died, in the following year the strength was 50,702 and of these 14,045 were admitted and 429 died.

In 1918 in the Macedonian Expeditionary Force 24,245 were admitted for dysentery and 480 died out of a total strength of 128,747.

Again let us compare these figures with the Italian returns of their late expedition in Abyssinia. As stated above the force numbered 500,000. There were 453 patients admitted to hospital on account of dysentery and only one died. This death occurred after the war was over and was ascribed to pneumonia. By

analogy with the figures above we should have expected 80,000-100,000 cases and between 3000 and 4000 deaths

Next, *enteric fever* In 1881 the strength of the French troops in the war in Tunisia was 20,000, cases of typhoid fever numbered 4200 and deaths from it 1039 In the Spanish-American War of 1898 the American troops in Cuba numbered 107,973, in a little over seven months there were 20,738 cases of typhoid fever In the Boer War, out of the British strength of 200,000 there were 59,750 cases and 8227 deaths

In the Italo-Abyssinian War the disease was 'practically absent' from Somaliland and the same is recorded for Eritrea Altogether there were 458 cases and 161 deaths—remarkably few cases but a high fatality rate (35.1 per cent) Had the prevalence been as great as in the South African War, for example, among the British troops, there would have been some 100,000 cases and several thousand deaths The mixed tetravaccine was used, *viz*, typhoid, paratyphoids A and B, and cholera

Typhus fever was responsible for a terrible epidemic among the Serbian Army in the Great War, some 25 per cent of the troops being destroyed by it Among the Abyssinian troops, the Italians stated, there were "at least 20,000 cases," but among their own not a single case because of the rigorous cleanliness enforced It was exceptional to find a soldier with lice Of *relapsing fever*, another louse-borne disease, there were in the Abyssinian Army between 20,000 and 30,000 cases [wide limit], in the Italian force only 17 cases, none of them fatal

In the Mesopotamian Expeditionary Force in 1917 there were 6242 cases of *heatstroke* and 524 deaths, whereas among the Italian troops in Abyssinia in 1935-6 there were only 30 cases, 7 fatal In the latter war every soldier had a sun-helmet, no alcohol was permitted, not even a glass of wine, till after sunset, marching was avoided as much as possible, so that the men did not suffer from fatigue through carrying arms and equipment, the troops being conveyed from place to place by motor-lorries

Scurvy was in former times, like dysentery, a veritable scourge of armies, and in the Italo-Abyssinian War, according to the Ethiopian Red Cross authorities, there were over 30,000 cases of this disease on the Somaliland front Arrangements were made for every man in the Italian Army to have a lemon a day, there were no cases recorded among them [Throughout the foregoing the figures of the incidence of disease among the Italian troops are from returns rendered by their own medical officers]

The following summary is too eloquent to call for comment.

In 1890 the French in Tonking lost by disease 1125 out of a total of 8505 white troops, or 13·2 per cent. In 1895 in the French expedition to Madagascar almost one-third of the white troops died of disease, 3417 out of 9600 in the Army (35·6 per cent) and 772 out of a naval force of 3250 (23·7 per cent), or together 4189 out of 12,850 (32·6 per cent).

In 1900, in the South African War, between March and September, there were 5219 deaths from disease among 190,000 to 200,000 troops (other records give the total strength as 154,000–186,000). At Ladysmith there were 13,496 white troops and in the four months, November 1899–February 1900, 10,668 were admitted to hospital.

In 1916–18 the average strength of the East African Expeditionary Force was 50,000, of these 2794 were killed in battle or died of wounds, and 6308 died from disease, *i.e.* 56 per thousand died from the result of the fighting and 126 per thousand from disease.

In 1935–6, in the Italo-Abyssinian War, 1099 of the Italians died in battle or from wounds and 599 only from disease (including accidents). The records of the Italo-Abyssinian War are valuable as indicating the results of the application of known preventive measures in a modern expeditionary force as compared with the prevalence of disease in an army fighting under the conditions of a century or so ago, when practically no preventive measures against disease were undertaken.

The following is a statement by an eye-witness written in a letter from Addis Ababa in July 1936.

In the Abyssinian Army diseases [that is, cases of disease] were very numerous, more than half the cases were dysentery, scurvy destroyed the army on the Southern Front, smallpox decimated the army of Mulughietta on the Northern Front. At Dessie pneumonia was raging. The terrible disease typhus was passing from one camp to another killing the victims in a few days. Malaria and relapsing fever were common. Women and children in thousands accompanied the soldiers to the front, but only a few returned, the others being killed by disease.

It is obviously no exaggeration to say that one of the prime reasons for Italian success was the combined health of its armies due to the efficiency of its medical service. It also might be observed that medical science made it possible for people to live in unhealthy climates under adverse conditions and to remain in better health than natives acclimatized by hundreds of years of continuous abode.

In conclusion, we are fully justified in saying that advances in military hygiene have not benefited the Army alone, the benefits to science have been mutual and reciprocal. The needs of the

Army stimulated research and the results of research conferred blessings inestimable on the Army. During a time of stress, when in former campaigns hygiene had failed, in the Great European War she came triumphantly into her own.

At the same time it is a fact fully acknowledged by the Medical Service that co-operation of the rank and file is necessary. All the advice and recommendations in the world will be ineffectual if the combatant does not comprehend in some degree at least the reasons for their application and so assist in their being carried out. As Sir J. A. Hartigan, Director-General of the Army Medical Service, wrote in his report on the Health of the Army in 1935 :

Sanitation in the Army is largely a question of discipline, no soldier is allowed to live in dirty surroundings or to ignore the practice of *personal cleanliness*, and it is noticeable that wherever a unit maintains good discipline its sanitation is of a correspondingly high standard.

CHAPTER III

THE COLONIES, PROTECTORATES AND DOMINIONS

We will now proceed to place before readers, as briefly and concisely as the immensity of the subject will allow, pictures of the state of things as regards the conditions of the people and the prevailing diseases to which they were liable in the tropical and subtropical colonies and similar parts of what are now the Dominions a century or a century and a half ago

Spaniards and Portuguese were the pioneers of *modern* colonization, the former exploring and settling west, the latter mainly in the east. Though this holds roughly, we must bear in mind that the best Portuguese colonization was west, Brazil, and that of Spain east, the Philippines. Prince Henry of Portugal, the navigator, may rightly be regarded as the 'father of modern discovery and colonization'. He, as a fact, was half English, for, though his father was a Portuguese king, his mother, Philippa, daughter of John of Gaunt, was an English princess. The Portuguese were probably the first of European nations to grapple with the real problem of African colonization by direct government control. Other nations left African affairs in the hands of merchant adventurers or private persons.

The French have always been good colonizers. They have enterprise, they can fight on occasion (sometimes, like the Irish, without it) and, most important of all, adapt themselves to new countries and new people. They treat the natives with humanity and with consideration, they organize them, form alliances with them, and knit them together as did Duplex in India and Champlain in Canada. On reading their history we see the reason why they have, to a great extent, failed to maintain the position these merits, these traits, these characteristics deserve. It is because they attempted too much and their energies were divided between colonial extension and European conquest and because of religious intolerance.

Britain, from her position, has had many advantages and one

of inestimable value for exploration and colonization—her insular position This fact has made her a nation of sailors She has had practically no interference on the Continent since the loss of Calais in 1558 (though Dunquerque was held a century later for a few years, 1658–63) Her insular position, moreover, invites commerce Her peoples are of mixed races—English, Saxon, Jutes, Danes, Norsemen, Flemings and others Her explorers are household names—Frobisher, Willoughby, Chancellor, Davis, Hawkins, Drake, Raleigh, Cook, to mention but a few Great Britain is an excellent example of a country which has, paradoxically, gained by her losses In the Middle Ages she tried to become mistress of France, now all that is left of that are the Channel Islands Had she obtained her wish and won France and thereby become a continental power, she would have lost the advantage of her insular position, less of an advantage now than in the days prior to aviation, but still not a negligible advantage, and with a divided front her energy would have been dissipated, leaving little for colonization Again, in the eighteenth century she lost her American colonies, but she found Australia and learned from her western experience that forcible coercion does not retain a friend

Volumes could be, in fact many have been, written on each of the colonies and our remarks will, therefore, have to be very condensed—a mere sketch

Warm countries were, it is probable, the original headquarters of man What drove men to leave tropical lands where there was abundant food and no need of clothes or fire for warmth, to live in countries cold, inhospitable or, to say the least, uninviting for half the year, is a question interesting perhaps but not very fruitful because insoluble Many will think that it was the pressure of disease, at all events in some measure, for disease naturally flourishes in warm climates—all kinds of animal life, disease germs, their insect hosts and transmitters, are stimulated by the heat and moisture The cold of the temperate zones would kill many of these (for example, yellow fever died down in the United States in the cold months) so that the life of man, even if more difficult in many ways, was nevertheless safer

Whatever may have been the proximate aim of our early colonizers the specious reason regularly associated with the enterprise was enlargement of the bounds of Christendom We find this expressly recognized, for instance, in the charters given to Sir Humphrey Gilbert and to Sir Walter Raleigh When in 1627 Barbados was granted to Lord Carlisle the charter informs us that it was for “propagation of the Christian faith” as well as

for the "enlargement of His Majesty's dominions" It is not until the rough preliminary work of planting and building up a colony has been accomplished, or is at least well on the way, that we come to feel by degrees a sense of the moral responsibilities which are imposed by Empire It was only when the British colonizers came to survey the result of their work that they were able to realize adequately the duties involved in such a heritage as they had acquired

AFRICA

We will begin by offering a sketch, a skeleton or outline picture of Africa and its chief tropical colonies when the British first became acquainted with the country in the earlier pioneering days Our remarks apply to West Africa, for East Africa when taken over after the Great War was in a more advanced state of civilization

Travellers exploring new tropical country, penetrating into what was to the European truly virgin soil would find, before the days of cultivation of the land, that rivers had become choked and had overflowed their banks in seasons of rain, creating vast marshy areas, in other parts thickets and brambles spread till they were almost impenetrable, forests so dense that the rays of the sun could not enter, that trees had fallen and were rotting where they fell Months, nay years, would elapse before the marshes could be drained, rivers guided and channelled, forest and bush cleared, earth ploughed and agriculture properly directed, before the white man could settle and put industrial undertakings in motion

We have but to read, or recall the readings of our younger adventurous days, in the works of Mungo Park, David Livingstone, Henry Stanley, Lovett Cameron and Mary Kingsley, to name but a few, to get some idea of the difficulties and troubles of the pioneer explorers and the diseases with which they had to contend in days when little indeed was known of the mode of causation and the means of prevention

Mungo Park who travelled, explored and was a captive in the interior of Africa, states that while crocodiles are not uncommon in the Niger they are of little account compared with the amazing swarms of mosquitoes which came from swamps and creeks in such numbers as to harass even the most torpid of the natives

I usually passed the night [he says] without shutting my eyes, walking backwards and forwards, fanning myself with my hat Their stings raised numerous blisters on my legs and arms, which, together with the want of rest, made me very feverish and uneasy

He did not know that they might be the transmitters of disease, malaria among them, and that this rather than the mosquitoes *per se* was the cause of his fever. When a prisoner in Ludamar, Gambia, he noticed that the chief diseases were intermittent fever and dysentery, the latter generally being left to cure itself. He was told, however, that smallpox was at times very destructive, prevailing amongst some of the Moorish tribes and by them conveyed to the negroes in the Southern States. Dr Laidlay (sometimes spelt Laidley), who was in practice out there, informed him that the negroes in the Gambia practised inoculation, using a thorn or a knife- or dagger-point for inserting the matter from a variolous pustule. The Mandingoes, a tribe leading an active life on a simple diet, suffered but little—mainly from fever and fluxes. The latter they treated, usually without success, by various tree-barks powdered and mixed with the patient's food, for the former they made an ingenious sort of vapour bath.

On the first attack of a fever, when the patient complains of cold, he is placed in a sort of vapour, this is done by spreading branches of the *Nauclia orientalis* upon hot wood embers and laying the patient upon them, wrapped in a large cotton cloth. Water is then sprinkled upon the branches, which [Park is often hazy in the use of his relative pronouns] descending to the hot embers, soon covers the patient with a cloud of vapour, in which he is allowed to remain until the embers are almost extinguished. This practice commonly produces a profuse perspiration and wonderfully relieves the sufferer.

He mentions other diseases prevalent among the negroes, such as yaws, elephantiasis and leprosy. From his description this last seems to have been true leprosy and of a rather acute type. Guineaworm infestation (*Dracunculus medinensis*, according to present nomenclature) was common, he states, in certain places and especially at the commencement of the rainy season. He probably meant the end of the dry season when the waters were low, for this is the time when the Cyclops, containing the larvæ, is most likely to be ingested, the sick and infested Cyclops sinking to the lower strata of the pools and man dipping low for water in the drying pools. The course of development to maturity in man is long and it is usually about a year after ingestion before the adult appears beneath the skin of the leg and declares its presence. The acuteness of observation by the natives is exemplified in their attributing the disease to bad water and alleging, as is quite true, that the people who drink water from wells are more liable to it than those who drink from streams.

Abscesses were common and it is worth noting that the negroes of Africa anticipated modern surgical methods by opening them with the actual cautery. Goitres were frequently seen among some of the tribes he met, especially in parts of Bambara, these also the natives attributed to the water. Mention may be made here of a curious method of cupping (other travellers also speak of it) employed for treating localized inflammation. The part is incised and the operator applies over it a bullock's horn with a small round hole in the pointed end. He takes a piece of bees'-wax in his mouth, puts his lips to the hole and sucks the air from the horn, he then by a skilful movement of his tongue stops the hole with the wax. The method is said to answer its purpose well and to produce a plentiful flow of blood. Park was repeatedly ill with fever and even more often with dysentery. Once, feeling himself getting very weak and failing, he took large doses of calomel till it set up so severe a stomatitis that for six days he could not sleep or speak, but the dysentery cleared up.

Commander Lovett Cameron in his book *Across Africa*, describing his experiences some sixty years later, shows that the conditions in his time were much the same and the hardships no less. He himself suffered repeatedly from fever, dysentery and abscesses. Moffatt, his lieutenant, died and his name is worthy of inclusion in the glorious roll of those who have sacrificed their lives in the cause of African discovery—a roll which contains the names of Mackenzie, Tinné, Mungo Park, van der Decken, Thornton and Livingstone.

Cameron notes that at Ugogo, country even then under cultivation, at the hut entrances were many showing actual smallpox rash, a disease which, he states, sweeps at times like a devouring fire through large portions of Africa. He suffered from eye trouble, inflammation which he attributed to the glare and dust, but in one place he mentions that only after five weeks was he able to write again, because he had been "quite blind and very bad with fever," for which he took abundant quinine. From his own account this appears very likely to have been quinine amblyopia, at least in part. Out of forty-five consecutive days he was free of fever on sixteen only, one of his staff, Dillon, had fever every day but, he adds, not violently, "what I am most afraid of is his sight. He has quite lost the use of his left eye and has occasional symptoms in his right. It is atony of the optic nerve." One wonders how he knew this, as Cameron was not a medical man, it is true that in quinine amblyopia there is marked pallor of the disk, though modern experimental work has led to the conclusion

that constriction of the retinal vessels is a subsidiary cause, the primary being the toxic effect of quinine on the ganglion cells of the retina. Speaking of himself he states, "These horrible fevers and blindness quite prevented my doing anything since I last wrote and my eyes are now anything but perfect"

It is remarkable that he and his party did not suffer from relapsing fever, perhaps he did, but his descriptions of his repeated attacks indicate malaria rather than relapsing fever. He notes that the dwellings were infested with vermin, the worst being enormous ticks, "the bite of which is so annoying that the Arabs believe them to be venomous and often to cause fevers". We cannot wonder that louse-borne disease was common among natives whose method of hair-dressing was laborious, occupying two or three days, but when once done it was allowed to remain undisturbed for six months or even longer. His book contains constant entries of his being down with fever and dysentery and on one occasion, when thus *hors de combat*, his condition was aggravated by Sambo, his boy, mixing the dough for his breakfast cakes with castor oil.

Large mosquitoes were constantly biting in the daytime and my back was covered with boils (possibly the biting insects were *Stomoxys* or even *Glossina* (tsetse)). He could neither sit nor lie down in any comfort and his feet were sore from bites and abscesses. My state was not altogether enjoyable.

He tells of the peculiar localization of malaria, or perhaps one ought to say that he remarks on its absence in places where one would expect the disease to prevail. At Nyangwé, the settlement of the Zanzibar traders on the Lulaba, situated on the right bank of the river, there was no malaria nor, so far as he could see, other fever, the left bank being lower was overflowed annually by floods which on receding left "festering, stagnant pools". Nevertheless the Wagenya tribe live there and flourish and apparently feel no ill-effects from the miasma. If this still holds good, an estimation of the splenic index in the district would be very interesting.

On Lake Tanganyika his travels brought him to a narrow channel into which the River Ngomanza flows. It was the common local belief that whoever drank of the water for a week or ten days became a leper. He observed that the majority of the people there were leprous, having lost a hand or foot, or being blind in one or both eyes. They are forbidden to emigrate, he says, and none of the neighbouring tribes will intermarry with them.

On another occasion he says that he began to suffer from

excruciating pains in head, back and limbs and on going down to a stream to bathe found on his body many purple spots and that a slight bruise on his ankle had become large and angry-looking. On attempting to light his pipe he found blood on it and his gums were soft and bleeding. He was clearly suffering from scurvy and was hurried to Benguela in a hammock. On arrival his tongue was swollen, he could not speak or swallow, his body, we are told, was covered with blotches of a variety of shades of purple, blue, black and green while the rest was of a deadly pallor.

In the Lulaba district and Lake Kassali—a limestone formation, it may be remarked—the people were much afflicted with goitre and the idea was rife that strangers residing among them were likely to develop symptoms after drinking the water for a few days.

Cameron concludes his interesting narration by suggesting for the help and comfort of future travellers that depots or stations be established on a trunk route across the continent where the explorer may find a resting-place and fresh stores. By starting from both coasts a chain of such stations some 200 miles apart might be established in a comparatively short space of time. When he made these suggestions he must have forgotten temporarily the experiences of pillage and banditry through which he had passed or he would have said something about the likelihood of such depots being plundered by marauding bands of natives.

We will now pass another interval and come to the last years of the nineteenth century and the early years of the twentieth and hear what that remarkable woman and intrepid explorer, Mary Kingsley, has to tell us of the West Africa of her day. She remarks that the life of the white man in any but the main towns and centres is terrible and monotonous, deprived of European society, his sole outlook the forest, the river and the beach, while the West Coast climate is bad for all but the native. We shall see later that this does not hold good now and it is more than probable that the monotony, bad habits, self-indulgence and loss of morale had more to do with ill-health in her day than the climate *per se*. Miss Kingsley found, as all have done who have lived and worked in the tropics, that the native will usually say what he thinks you will like to hear, perhaps out of politeness, perhaps to ingratiate himself, and that his every statement must be verified. At Fernando Po she asked about the water for drinking and was assured that it was perfect—beautiful spring water coming down from the mountain. The same day she had occasion to go up the mountainside to Basile and the final part of the journey happened

to be along the course of the stream from which the water for drinking was taken She writes

The first objects I observed in the drinking water supply were four natives washing themselves and their clothes, the next was the bloated body of a dead goat reposing in a polluted pool The path then left the course of the stream, but on arriving in the region of its source I found an interesting little colony of Spanish families which had been imported out whole, children and all, by the Government They had a nice neat little cemetery attached, which his excellency the doctor told me was stocked mostly with children, who were always dying off from worms Good, so far, for the drinking water! and as to what that beautiful stream was soaking up when it was round corners—I did not see it, so I do not know

She is very lugubrious and pessimistic as to the outlook of those who go there

Remember, before you elect to cast your lot in with the West Coasters, that 85 per cent of them die of fever or return home with their health permanently wrecked Also remember that there is no getting acclimatized to the Coast There are, it is true, a few men out there who, although they have been resident in West Africa for years, have never had fever, but you can count them up on the fingers of one hand There is another class, who have been out for twelve months at a time, and have not had a touch of fever, these you want the fingers of your two hands to count, but no more By far the largest class is the third, which is made up of those who have a slight dose of fever once a fortnight, and some day, apparently for no extra reason, get a heavy dose and die of it A very considerable class is the fourth—those who die within a fortnight to a month of going ashore

She noted that the African natives seemed very prone to suffer from rheumatism, whether the climate was that of the reeking Niger Delta or the dry and delightful climate of Cabinda

Up to the end of last century and even for the earlier years of this the West Coast of Africa had an evil reputation A Handbook of Useful Information was published and among the matters dealt with were "How to reach West Africa and how to return," and the second part began with the statement, self-evident, though not grammatically expressed, "If dead, this will not be needed" There is an old saying that outside Sierra Leone the bones of those dying at sea from malaria or yellow fever were popularly believed to be so numerous as to impede the boat, the reason being that old residents when starting on the voyage home would feel the welcome north-east breeze as the boat rounded Cape Verde and would throw open their shirts, catch a chill, a relapse of malaria or of blackwater fever would follow and result in death in 24-48 hours or so

Insurance companies were frightened and would immediately cancel a policy if the holder notified them that he was off to the West Coast. The newcomer was cautioned not to venture out before the malaria mists had cleared in the morning, nor on any account to stay out when they appeared in the evening, while to go out, at all events to stay out, in the heat of the sun's rays would be fatal. Can we feel surprise if the monotony and confinement drove the settlers of the day to cards and drink?

The foregoing remarks have been of a general character, a few may now be made on the African colonies separately, starting with West Africa.¹

The part of West Africa with which Europeans are best acquainted is a strip along the coast starting some 200 miles from the mouth of the Gambia and extending to Lokoja on the Lower Niger, but even now, after four centuries of trade, there are parts with which our acquaintance is small—vast tracts, hot and steamy, with dense forests, muddy rivers and ‘wastes of quaking swamp’. A land of plague and pestilence, if not of famine, where Juju and superstition reign and render the life of the native one of constant menace and dread. Northerly, this land of primeval forest passes to a drier soil with gums and acacia, plume grass and isolated woods till we reach the desert.

Egyptians, Carthaginians and Romans were persuaded that the wilds of north-west Africa were traversed by a river flowing east to the Nile and west to the Atlantic. Explorers for many centuries strove to elucidate the mystery, but one after another met his fate in death by thirst or sickness. The pioneer in early days in very deed carried his life in his hands and found almost certain martyrdom, and that not a spectacular one, but walking daily, hourly, in the depth of the forest gloom, within the shadow of death, in a barbarous land, and usually, when he was helpless he was deserted by his servants, left at the mercy of swarming insects, prowling beasts, or to a long-drawn-out agony of death from hunger and thirst.

Later, when settlements near the coast were attempted, the new arrival, the hopeful settler, would be faced with miry creeks and mangrove swamps beyond which was a network of more creeks and waterways, with a miasmatic haze pierced with tufts of oil-palms or giant cotton trees, and this steaming atmosphere, this malaria-haunted haze, would prevail during most of the year, dispelled for a short time by the welcome harmattan. Among

¹ Much useful information of a non-medical nature is contained in the book by Harold Bindloss, *In the Niger Country*, Blackwood, 1898.

this welter might be small collections of wooden buildings, factories erected on piles with mud wastes behind and the tide in front. The difficulties of erecting even such dwellings as these were very great. When the site had been selected and possession obtained, it was then that the real trouble would start. The muddy swamp had to be made more stable by the flinging in of canoe-load after canoe-load of sand brought from the bar, until it would bear supporting piles sufficiently firmly to prevent them being borne away by the tide. Bindloss writes

Now legions of marine worms with things resembling diamond drills in their heads, and molluscs with razor-edged shells riddle the piles which cave in suddenly, or boring crabs take up their quarters in the sand. They tunnel it from end to end until whole square yards of it sink away.

Can we imagine that when we nowadays visit any of the prosperous, almost healthy coastal towns, their sites were once like this?

Back in the adjacent Hinterland the forest gives place to mangrove swamps (well described by Lander in his book of travels and the account of his expedition after that of Clapperton) with here and there, on patches of more solid ground, rickety dwellings, mud-walled, or built of reed-mat and sticks, perched as it were over a muddy streamlet or ditch into which excreta fall and refuse is cast.

Such were the conditions with which the pioneers had to contend, it was on a basis such as this that education had to be grafted, amid such fever-ridden spots that sanitation had to be installed and superstition met. Superstition is natural to all natives and is more rife, more soul-destroying probably in the tropical bush natives than elsewhere.

Dwelling in the shadow of the primeval forest or swamp-land, grotesque and horrible as the creations of a nightmare and swept by pestilence, it is nowise strange that the negro should people the steaming bush with malevolent deities. Danger continually threatens him and he is ever face to face with death. Mysterious sicknesses decimate the stockaded towns, legions of venomous insects lie in wait among the brushwood and sand. Poisonous snakes, centipedes, and spiders worse than either crawl into his huts, scaly alligators lurk in the mire of the fords, thus he creeps through life in superstitious terror, and in each mysterious rustle of the palm fronds when the bush lies still at night he hears the voice of evil spirits breathing spells upon the forest — (Bindloss)

Let us not, in the comfort of our civilization, ridicule this as the mere imaginings of ignorance, an exhibition of cowardice, the

promptings of guilty conscience The white man going to these lands from his modern comfortable home comes in time under the spell if his lot takes him to a lonely district To a visitor or a newcomer it is an interesting experience to watch a game of cards in a factory or at the house of one of these older residents One will bring out the tooth of an animal, an alligator perhaps for choice, with characters carved or graven on it, another produces a quaint carving in wood or bone, to bring luck or, as some believe, as a mascot to ward off sickness Those who have lived in the place for some time take this all for granted and make no remark, but should the newcomer ask the reason, the talisman may be put away, but not abandoned, with a blush or a jest, or kept out with a remark of half shamefaced bravado

This, however, only shows itself, openly at least, in off-moments at times of relaxation from sterner duties The Anglo-Saxon has a wonderful knack, nay rather there is a characteristic more developed in him than in any other race, of rising to the occasion when confronted by difficulties The young official, fresh from a home of comfort, perhaps luxury, carefree and happy-go-lucky, finds himself, as he would say, up against it, confronted by discomfort, privation, awkward situations, danger, perhaps for the first time We see him transformed into the quiet, thoughtful, grim person, making rapid decisions, carrying out his work to the best of his ability, and therefore efficiently, placing his work, his calling, his profession above personal considerations, content to be a cog, so long as he is an efficient cog, in the administrative machinery, provided he is the right kind of man, and the majority belong to this category either from the first or soon qualify for admission to it The other kind either promptly throws up his work in disgust or striving against impossible odds is quietly and unobtrusively 'invalided' home

It is not altogether cheering for the newcomer, or the aspiring official, to read the following which appears in a medical treatise which was in circulation at the end of the last century on the West Coast, telling him what he must expect to encounter or suffer from

Shivering, lassitude, headache and backache Cerebral excitement with raving delirium Liver deranged—constant vomiting Vomiting of blood Chronic hæmorrhage, Blackwater, shivering and rigors Sun-stroke with staggering and unconsciousness Acute dysentery Asiatic cholera Acute jaundice Typhoid

The author of this comforting tome might have added, with more truth, the driver ants which, when they invade a dwelling, make the inhabitants flee for dear life, for they come not single spies

but in battalions and wipe out every living thing in their way—rats, centipedes, snakes The natives will tell of sick men unable to get away being picked to the bone

A man in health can withstand great changes of climate and the fiercest tropical heat, so long as the humidity is low and he can get about It is the heat *plus* moisture, the clammy hot-house temperature day after day that makes exertion impossible and life miserable, and if, as is common at certain seasons in the tropics, the temperature and humidity persist with little change during the night also and prevent sleep, then the newcomer, arriving at such a season after a healthful voyage, feels himself crushed out of existence, life insupportable, unless relieved by artificial stimulus, drink or drugs If these be the effects in health, how much more oppressive for the fever-stricken

Perhaps the picture of the past has been painted in too sombre colours In the earliest days conditions were indeed bad, they could hardly have been worse, in the Niger Delta, but there came a period of development and improvement Coming down from the north through league after league of fertile land were established plantations of indigo and cotton along the river-banks, the marshy, tangled waterways of the delta would give place to drier soil which responded well to cultivation, until, as at Sokoto, there grew up fields of maize, barley, wheat and tobacco In other places, as at Bonny, the conditions on one bank of the stream differed from those on the other On one side were swamps, ooze and mud, on the other trading factories on dry land rescued from the forest of cotton-woods

So much for general description, a few words may be said on separate colonies to illustrate some of these points

It was in 1481 that Portuguese explorers came to the *Gold Coast* and passed as far as the swamps of the Niger Delta They were followed by the Dutch Not until 1872 did it become British, in return for concessions in the Java seas Lying between the Gold Coast and Ashanti is a varied range of country with forests, swamps, slowly flowing rivers and foul lagoons The British, a couple of centuries prior to this, had been attracted to West Africa by trade in spices, later gold and 'black ivory' (slaves) proved more profitable, especially the last (see later, Slave Trade)

At the time when Thompson sailed for the Gambia from England in 1618 the Gambia was thought to be the Niger It was the slave trade carried on with vigour and success by Sir Richard Hawkins—hero, buccaneer, slaver, and withal a fervent Christian—that provided the proximate goad to Europeans exploiting the

commercial possibilities of the West Coast Wrestling from the Niger country its secrets was not easily accomplished Leyland tried it and perished, Horneman, after passing from human ken into the Sudan, was heard of no more, Lucas came back an invalid, Houghton, trying from a different direction, from Senegal by a western route, in 1791 died of starvation, Mungo Park, already spoken of, reached the Niger itself four years later Ten years after he made an expedition, like Houghton, through Senegal, leaving Goree in 1805 with thirty-six white men Within a short time all had died except one white officer, two sick soldiers and a raving lunatic He himself, in unremitting conflict with starvation and hostile natives, perished by drowning when his boat struck a rock in the rapids as he was trying to escape from the fire of the natives on shore

Discoveries were, in despite of all this, being made, fact after fact was added to the sum, though at heavy cost—the deaths of Peddie, Oudney and Laing By 1830 Clapperton, after proving that the swamps of Benin were the delta of the Niger, died in Hausaland, Lander, his companion and servant, continued the exploration, but himself died four years later at Fernando Po In the early 'fifties Laird set up trading-posts along the creeks of the river The difficulty of establishing these has been mentioned already, and even after being established they were constantly threatened and sometimes demolished by raids on the part of the natives, or desolated by disease and accident Appeals were made on several occasions to the Government for help, but little or no regard was paid to them, so the factors took up matters for themselves and joined their factories to form the National African Company In 1885 a Protectorate was proclaimed and in the following year the company was granted a charter as the Royal Niger Company For more than a quarter of a century after this the district was, from a health point of view, highly undesirable A clammy, hot mist, dealing disease and death, prevailed for much of the year, owing to the proximity of swamp, undergrowth and forest At the end of last century many of the natives were cannibals, their religion that of devil-worshippers shackled by an oppressive superstition

We, a civilized nation, in the early days did not a little harm, partly in thoughtlessness, partly from greed and desire for wealth For fully 200 years we took the lion's share of the profits of the slave trade, later, we sold rum and gin to the native—in short, our record in the early days was none too clean Later, and unremittingly, Great Britain has done her utmost to retrieve her

reputation in these respects, to benefit the native, to improve his conditions of life, to look after his health and the welfare of his children. Government officials give the best years of their lives in beneficial administration, and not infrequently sacrifice health and even life itself in so doing, while missionaries use their utmost endeavours to help them, not only morally, but in tending to their physical welfare. At the same time the trader has improved beyond recognition when compared with his predecessor of the early days, at that time the majority were dissolute and dishonest, outwitting, whenever he could, the trusting native. Now, he is self-respecting and therefore respected, trusted by the natives and prosperous in proportion as this trust is not betrayed.

The difficulties in the way of development of the African colonies, the obstacles to successful trading, have been very real and very great. Reeking marshes, mud-silted rivers, insect-haunted swamps, dense forest, almost impenetrable from closely matted growth of creeper and cruel obstructing thorn, any huts erected soon became the haunt of ticks, flies, mosquitoes, spiders and scorpions. Rivers and streams had to do duty for roads, but transport might be held up for weeks by silting and choking of these by mud. The only alternative was native head-porterage by narrow tracks which had to be traversed in single file. Now we have better harbours to facilitate embarking and landing of goods but there is need of more, landing through a fringe of breakers is a hazardous and a tardy procedure. There is need of light railways for transport to and from the interior, to save endless dilatory files of native bearers winding their way slowly through the country. It used to be said with regard to Nigeria "Gin, Manchester cotton, salt, Government officials, young trading clerks, brought to fill the gaps made by illness and death, go in; rubber, palm oil, kernels in immense quantities, and broken down invalids come out." Under British rule Lagos attained, in spite of its climate of ill repute and of the loss by invaliding and death of officials, remarkable prosperity, in fact, because of the commercial activity of the port, it was spoken of as the Liverpool of West Africa.

We are inclined to forget that the native cannot be civilized in one or even two generations and thus we expect too much from education. Even the best of them, sent over to England and educated there, instilled with Christian ideas, may lapse again within an interval not very long, into his earlier state, provided his environment is conducive to it. These remarks are not intended in any degree to belittle the wonderful work which the missionaries

carry out, the medical missionaries in particular, who not only treat and cure their diseases, but also seize any favourable opportunity to instil the principles of hygiene. There can be but little doubt, however, that almost any negro race will both accept and lose the tenets of Christianity very easily'. His conversion, we have been told, is not very difficult, but with equal facility he may pass back to superstition and his former ideas of right and wrong, of *meum* and *tuum*. Thus, it is recorded that Jinga Bandi, a chieftainess of the Kongo royal family, came to Loanda and, becoming friendly with the Portuguese, was persuaded to be baptized. On returning to her own land she found her brother reigning as chief or king of Angola. Without any obvious qualms of conscience she promptly poisoned him to obtain the throne for herself. It is but fair to say that on the other hand the results of *permanently* rooted Christianity are clearly shown in the two or three millions of really good negro men and women to be found in the United States, the West Indies and Cape Colony (Johnston).

There are in Nigeria three forces at work, two beneficial and one the opposite. These are the British Government as the Niger Coast Protectorate, the Royal Niger Company, and the third, inimical, Juju, the power behind the throne in much of West Africa. The first, by its administrators, its consuls and vice-consuls, do all they can to keep trade routes open and to suppress bloodshed and sacrifice, while the second administers trade over extensive areas.

It is a characteristic of British colonization that when we undertake the opening up of a new country we are content, when humanly possible, to hold the trade by the quality of our merchandise and low prices, while any native is at liberty to find a market there, other countries, some others at least, when establishing a Protectorate, start by driving out the traders of other countries by tariffs and duties. Maybe this is one of the reasons for the success of British colonization.

There is little to add regarding other colonies and protectorates on the West Coast because what we have said above of Nigeria and the Gold Coast applies largely to them. *Sierra Leone* in the early nineteenth century was in a like woeful state and fever-ridden. In the middle of the century Dr W F Daniell wrote

Were it not for the fatal insalubrity of the climate, so deleterious to the European constitution when life is not forfeited at once, it is impossible to say what extent our commercial intercourse would have acquired with the inland regions of the vast continent of Africa which lie at this moment unexplored and unknown.

Freetown was described in no flattering terms as a Golgotha and a Gehenna, and Sydney Smith said on one occasion "There are always two Governors of Sierra Leone—one just arrived in the Colony and the other just arrived in England"

Sierra Leone has had a chequered history Towards the end of the eighteenth century it was established as a settlement for emancipated slaves from the West Indies and for others when disbanded in Nova Scotia after fighting on the British side in the American War of Independence, West Africa being regarded as a more congenial climate for them than that of Canada Included also were 400 masterless slaves in England—the so-called 'Granvilles,' because of the Granville Sharpe decision regarding the illegality of slavery in England—some Maroons from Jamaica, *i.e.* Cimaroons, troublesome outlaws living in the hills (*cimas* = heights), together with slaves liberated from captured traders, natives of West, Central and other parts of Africa, called as a class 'Willyfoss' negroes because their freedom was attributed to the efforts of Wilberforce Johnson relates that to crown their hospitable intentions the philanthropic authorities sent out sixty London prostitutes to 'make them into honest women' by marriage with the negroes Further, English, Dutch and Swedes were invited to go out as settlers on the idea that West Africa was, like Cape Colony and, later, White Australia, suitable for European colonization The natural, the almost inevitable, result was death from sickness and fever

During the present century Freetown, the capital of Sierra Leone, has developed rapidly, it has a good harbour, with palm groves and cultivations on the south and houses picturesquely situated among orange and lime groves with Tower Hill rising behind and backed by the still loftier Sierra To the north, however, in the early years of the century at least, was a vast swamp with mud and mangroves, covered for half the year with a heavy mist The town itself has a paved main street, well-built houses and offices, the former with verandahs and gardens The climate is hot and humidity high, malaria and rheumatism very prevalent Beyond the harbour area is the native quarter, poor huts amid squalor Education is progressing apace and natives have gone in for law and medicine and some have done well One drawback, and a great one, is that only a certain small proportion of natives can 'carry corn', where equality between black and white is aimed at Jack is as good as his master and it is not long before he comes to regard himself as 10 per cent better The transition stage in civilization of the negro is not all joy In his savage state

he may be bloodthirsty, and degraded by superstition, but he is often, apart from superstitious dread, fearless and, according to his light, honest, half-education takes the steel out of his nature and he comes to learn more of the vices than of the virtues of the European. Not uncommonly they abuse their privileges and pour their venom, in their native press, on hard-worked and harassed officials who are doing their best to raise the position and status of the native—a stupid and ungrateful return, for were it not for the presence of the European and orderly administration of a Government that affords them protection, they would ere long lapse and attacks from without by neighbouring bush tribes and from within by internecine strife would lead again to bloodshed, anarchy and, in some cases, to annihilation.

To class all the West African negroes together as barbarous and ignorant in those early days would be a grave mistake, barbarous perhaps but certainly not ignorant and even refined in art procedures. The Benin expedition at the end of last century discovered a remarkable art which had sprung up and developed in that city of blood, such as bronze castings in the *cire perdue* process, which may now be seen in the British Museum, and also really beautiful carvings in ivory. It is thought that the art of working in the metal was introduced from the central Sudan, the natives of which in turn had learned it from Arab craftsmen and traders and teachers from Egypt and Tripoli.

The more general results of civilization are nowhere more apparent than in French Senegal, here there are good roads through what were dense forests, built, it is true, at the cost of much sickness and many lives, and there is a good railway. The natives themselves have become clean and orderly.

The Crown Colony system has, as most people with knowledge will agree, certain drawbacks, as must every system of colonial administration. Mary Kingsley sums up the main difficulties and drawbacks with great acumen and wide view. She is speaking, of course, only of West Africa.

Our policy in West African Colonies has been described by a medical man as 'coma accompanied by fits'. This would not be the case if the Colonial Office had a definite detailed policy of its own and merely sent out men to carry it out, but this the Colonial Office has not got and cannot have, because it has not got the scientific and commercial facts of West Africa in its possession. It has, therefore, to depend on the Governors it sends out, and these are men of diverse minds. One Governor is truly great on drains, he spends lots of money on them. Another Governor thinks education and a cathedral more important, during his reign drains languish. Yet another Governor comes along

and says, if there are schools wanted, they should be under non-sectarian control, but what is wanted is a railway, and so it goes on and of course leads to an infinite waste of money Why not one Governor-General for West Africa? (But see p 91)

Let us now leave the West and say a few words concerning *East Africa*. Diseases prevalent in these, as noted by Livingstone in his travels and explorations were pneumonia, rheumatism, heart disease, smallpox, whooping-cough, dysentery and ophthalmia—a fairly formidable list. He also records malignant carbuncle which may prove rapidly fatal to those eating the flesh of animals dead of a disease “which is common in horses” to which, he says, “cattle too are subject but only at intervals, it may be of years.” He is mixing up horse-sickness and anthrax and the malignant carbuncle would arise from the skinning and not from eating the flesh of the animal. Diseases which he remarks as being absent are rather a surprise to us. “The prevailing idea of hydrophobia not existing within the tropics seems to be quite correct,” he states, nevertheless he records that a chief of the Bakwanis died after being bitten by a mad dog. Among this tribe he notes that there is no consumption and no scrofula. This was doubtless correct for his day, because at that time tuberculous infection had not been introduced. Cancer and cholera also, he says, are not known. Smallpox and measles had wrought terrible havoc throughout the country in the 'thirties. The former, he remarks, has repeatedly broken out on the coast but had not penetrated inland. The natives used inoculation for the smallpox but “adopt the vaccine virus readily when it is brought within their reach.” In one village where they seem to have chosen a malignant case from which to inoculate the rest, nearly the whole village perished. He concludes, “I have seen a few [cases] of epilepsy, none of cholera or cancer, and many diseases common in England are here quite unknown.” Incidentally, he gives a list of over a score of plants and their uses among the natives, some of these might well repay investigation. One was a substitute, and from Livingstone's account an efficient substitute, for Cinchona.

It is strange that he says little of sleeping sickness, negro lethargy, which subsequently became such a serious disease (see later, Chapter VIII), for he knew the tsetse well, in fact it is depicted on the title-page of his travels, he thought it harmless and would watch it bite him undisturbed.

Stanley also knew of the tsetse fly and mentions that its bite caused the deadly disease of nagana in horses and donkeys, but

he too found the insect harmless to himself—another species, we know now, conveys sleeping sickness to man

FEDERATED MALAY STATES

There is little to say of Malaya at the time these States were added to the British Commonwealth, *i.e.* at the latter years of the nineteenth century. Owing chiefly to rubber and tin they were prosperous, money was plentiful and, from the health point of view, was put to good uses. The time before that hardly comes within our scope, according to report it was “a land deep in the gloom of an evergreen forest whose darkness covered even darker deeds, for man fought with man and almost every man’s hand was against his fellows.” In a few years, says Sir Malcolm Watson in his work *Prevention of Malaria in the Federated Malay States*,

thousands of acres were wrested from jungle, thousands of people now live in peace and plenty, a railway stretches from end to end of the land, roads second to none bear motors of every kind, while chiefs who had never entered each other’s country except with sword in hand met in harmony

British administration has brought wealth and prosperity to a degree to which can be found no parallel. And with wealth has come health. From hundreds of square miles malaria, which formerly exacted a heavy toll from Malay and foreigner alike, has been driven out.

In 1900 there was established at Kuala Lumpur the *Government Institute for Medical Research*. Here were carried out the researches, now classical, of Braddon, Fraser and Stanton on the ætiology of beriberi which are described more fully in a subsequent chapter. The staff of the institute perform invaluable service in associating and bringing into close relation clinical and academic research, by studying the clinical aspects of disease, by carrying out research, and applying the latter in elucidating the cause and aiding in the treatment of the former. Apart from the dietetic researches of Fraser and Stanton in throwing light on a disease which threatened the well-being of the native, we need here merely mention the work of Stanton (later Sir Thomas Stanton, K C M G, Chief Medical Adviser to the Secretary of State for the Colonies) and William Fletcher on Meloidosis and of Lewthwaite and Savoor on Tropical Typhus.

The State medical service was conceived on broad lines from the very start, the duty of medical officers included giving advice on health matters and in safeguarding the well-being of employees, as well as attending them when sick.

It was in the Federated Malay States that the mosquito-malaria theory, as it was then designated, of Manson and Ross was put to the test by draining the town of Klang and in a couple of years the report was made that malaria was no longer of practical importance there (see later) Estate work is probably better developed in Malaya than anywhere else in the Empire Estates are well supervised and all of any size are concerned with the problems of housing, water-supply, conservancy, incidence of disease and its prevention, and so on

HONG KONG

Hong Kong became a Crown Colony in 1843, having been officially ceded to Britain by the Treaty of Nanking the previous year At that time Victoria, which is now the chief town, was little more than a barren rock, the few inhabitants living in ramshackle dwellings mostly constructed of relics of junks, and subsisting on their catches of fish In 1841-2 labourers came in greater numbers for erecting cantonments for the personnel of the Navy and Army and before long the place became a hive of industry, but unfortunately no attempt seems to have been made to enforce even the most elementary principles of hygiene, disease was introduced and spread rapidly A few figures will impress this fact In 1843 the troops numbered 1526, admissions to hospital totalled 7893, an average of rather over five admissions per man and deaths numbered 440 or 28·8 per cent of the total strength This must have been most disheartening and we cannot be greatly surprised at a report in a pessimistic vein of the Colonial Treasurer of the time "There does not appear to be the slightest probability under any circumstances that Hong Kong will ever become a place of trade" One who evidently had a more acute vision wrote at the same time in a newspaper, *The Friend of China*

For natural position few places in the world exceed this island provided all restrictions for a free intercourse with Formosa, with Japan, with Corea and with the coast of China beyond 32° North are swept away, Hong Kong in ten years as a place of trade will only be second to Calcutta

The latter was correct In six years the population increased nearly fivefold, from under 5000 in 1842 to 23,872 in 1848, and in less than half a century

In place of a bare rock with a fisherman's hut here and there as the only sign of habitation and a great sea basin very rarely disturbed by a passing keel, we have a city of closely built houses, stretching

for some four miles along the island shore and rising tier over tier up the slopes of the mountain while on the opposite peninsula of Kowloon [acquired by Britain on the mainland in 1861] and along the whole seaboard are numerous houses, together with docks, great warehouses and other evidences of a large and thriving population. Again, the silent and deserted basin has become a harbour so covered with shipping that even if a visitor had been round the whole world, he could never before have seen so much in a single *coup d'œil*. At anchor or moving are some forty to fifty ocean steamers, including ships of war, large European and American sailing vessels, and hundreds of sea-going junks, while in the space intervening and around are many thousand boats, for the most part human habitations, with steam launches rushing in all directions.

These are the words of Sir William des Voeux. For some years the tonnage returns for the port held the world record, exceeding even those of London and New York.

Nevertheless we cannot view the position entirely through rose-tinted spectacles. At the beginning of the present century the reputation of Hong Kong from the hygienic aspect was thoroughly bad. The density of the population was very high, 126 per acre, compare this with the administrative County of London with its proper sanitation, with density 60, Glasgow 61, Liverpool 50, Edinburgh 41. This, however, was but one feature, the water-supply was inadequate, roads were bad, drainage to all intents and purposes non-existent except for the natural fall of the hill-slopes, rents were excessive and food expensive. Dwellings were lofty but close together and many were in damp, dark alleys where no ventilation was possible and where the sun's rays could not penetrate, even at midday artificial lighting was needed—a most instructive example of a city being allowed to spring up and develop unplanned. Chinese and Europeans intermingled, Chinese shops and lodging-houses of a poor class would lie close to the private dwellings of Europeans. On the hillsides above the European residences were masses of native huts, overcrowded, unsewered, with no privies, and no means of removal of refuse. Excreta were deposited near the dwellings and left for the rains to wash away, as often as not into their neighbours' water-supply. Lower down the beach (there was no praya in those days) was grossly fouled by refuse of every kind thrown out from the near-by houses or brought down by the washing of the gullies from the hills. To one visiting the place only a few years later it would be inconceivable that such a state of things had existed, within a decade or so, although there remained overcrowded and badly or unventilated dwellings for the masses of the Chinese population (and there are not a few still), the mountain had been opened up,

good roads made, substantial and airy dwellings erected, good drainage and an excellent water-supply installed

Towards the end of the nineteenth and during the first twenty years of the twentieth centuries *plague* proved a serious scourge. Infection was probably introduced from Canton, but ere long Hong Kong, with so much traffic, became itself a fruitful centre of distribution and it is believed by many that India was probably invaded thence (but see later, Chapter XII, Plague). It was in Hong Kong that Kitasato discovered what he regarded as the bacillus of plague and to him and Yersin (who really did discover it) is given the credit, as their findings were made in the same year (1884).

We can but sketch briefly the progress of sanitation in the island. The high morbidity and fatality rates of the early days have been referred to above, the 'malignant fever' of those times was almost certainly malaria and from time to time rules regarding health matters were promulgated ending in 1856 in an Ordinance on the lines of those laid down by the London Board of Health. Ten years later a Medical Inspector of the Colony was appointed, whose duties related chiefly to sanitary administration. European sanitary inspectors were appointed some ten to twelve years later. In 1882 a Sanitary Department was formed with a Sanitary Board working under a Sanitary Ordinance. The Secretary of the Board, finding his duties as Sanitary Superintendent too onerous, a Medical Officer of Health was appointed as a relief. Amending Ordinances in 1903 and 1908 gave the Public Works Department supervision of water-supply, sewers and roads, while construction and alteration of buildings and the abatement of nuisances were attended to by a Sanitary and Building Board, with subsections to deal with medical, veterinary, engineering and secretarial questions. So effectual was this somewhat peculiar division of labour that before long Hong Kong was reported as 'the best scavenged city in the East'.

In 1906 a Bacteriological Institute was built, it was spacious, well equipped and with room for development. Here were undertaken the preparation of calf lymph, investigation of plague and plague-rats and later, after an outbreak in 1917-18 of cerebrospinal fever, the preparation of antimeningococcus serum. In the following year preparation of antirabies vaccine was instituted and this has proved most useful. Prior to this anyone needing treatment had to travel either to Shanghai or Saigon. Recently, with the growth of work carried on the necessity for enlarging the institute has called for structural changes and additions thus justifying the

wisdom of those who planned the original building with a view to the possible needs of subsequent development

Lastly, mention must not be omitted of the Hong Kong College of Medicine, started in 1887 by Dr (later Sir Patrick) Manson, which in time became merged in the Victoria University (see *Life of Sir Patrick Manson*, p 1072)

MAURITIUS

This island, which is about as large as Surrey, was, in spite of its natural advantages of situation and climate, permitted to go to the bad, medically speaking, from neglect of putting into effect the ordinary safeguards of health and from ignorance of scientific developments. There is one great disadvantage to which Mauritius is liable, namely hurricanes which at times work great havoc

Since the disastrous outbreak of malaria which followed the introduction of *Anopheles costalis* from Africa about the middle of the nineteenth century Port Louis was spoiled as a place of residence for Europeans—in fact, the whole coast-belt was rendered unhealthy. Time and again cholera also has been introduced, has gained a foothold and spread, owing to the local conditions which had been allowed to develop, favouring its becoming epidemic. The Rev Francis Flemyng, a resident in the colony in the middle of the last century, wrote

Were it not for the merciful and providential hurricanes [he, at all events did not regard these as an unmixed evil] which visit the island and thoroughly sweep and cleanse its surface and dwellings, the place would never be without disease, for a worse-drained and dirtier-conditioned place it has certainly never been our experience to visit among the colonial dependencies of Great Britain

And this was a place which had been looked upon as a paradise on earth! To speak truly Mauritius was going the way of India, the natives, the Chinese and the Indians lived, and were allowed to live, under the most shocking insanitary conditions, while the white residents had no eye to anyone but themselves, or anything but their own comforts, being too short-sighted to see that insanitation and disease among the poor was a constant and ever-growing menace to themselves

Osbert Chadwick, a sanitary engineer, was asked to advise concerning water-supply and disposal of sewage, and later Major Ronald Ross was requested to visit the island to point out the ways of preventing the ravages of malaria. Yet another disease,

ankylostomiasis, had become a veritable plague, the conditions under which the estate coolies worked, together with what was known as the *engrains* system, resulted in an infestation rate of 100 per cent in some districts

It is vain now to meditate on what might have been

The future never renders to the past
 The fond beliefs entrusted to her keeping
 Write this one sentence—Life's first truth and last—
 On the pale marble where our dust lies sleeping,
 It might have been !

How easy it should have been, seeing that the island was small and had but one port, to keep out cholera and plague, malaria ought not to have gained such a strangle-hold, hookworm infestation should and could have been checked by field-sanitation combined with treatment of those infested Enteric fever and dysentery, also prevalent, could have been controlled by a safe water-supply and proper methods of conservancy

From the viewpoint of material prosperity the Great War was beneficial to Mauritius, for a time at least she was well off and, wisely, a large sum was set aside for promoting health measures, but she had sunk so far in the slough that she has not been able even yet quite to emerge, the fight against disease and bad hygiene is long and severe *Facilis descensus sed revocare gradum, hic labor, hoc opus est*

WEST INDIES

Leaving the East and passing to the West, we need not consider the *West Indies* separately, they may be taken together Conditions of the towns, however beautiful the climate, were anything but inviting They would hardly be habitable were it not for the John Crows (the vultures) wrote one who knew Jamaica, the same remark applied elsewhere The vulture, the pig and the pariah dog were the scavengers, practically the only scavengers, so much so that the first was protected by law

The same was recorded by Waterton (*Wanderings in South America, 1812-24*) of Paramaribo, Dutch Guiana, and of Angostura, Colombia

I saw the vultures [he writes] as tame as domestic fowls, a person who had never seen a vulture would have taken them for turkeys They are very useful to the Spaniards and had it not been for them the refuse of the slaughter-houses in Angostura would have caused an intolerable nuisance

Some sanitary legislation there was in Jamaica, but it was not applicable to the towns. Each plantation had to provide one acre of ground well planted with provisions for every five negroes it employed, but the towns, even when well planned, and this was not common, were dirty and infested with flies. The conditions in Havana, Cuba, are described in the chapters dealing with yellow fever and may be referred to, generally speaking epidemics of malaria, yellow fever and smallpox were fairly frequent.

Richard Ligon, writing of Bridgetown, Barbados, early in the latter half of the seventeenth century, says

A town ill situate, for if they had considered health as they did conveniency, they would never have set it there, or, if they had any intention at first to have built a town there, they would not have been so improvident as not to foresee the main inconveniences that must ensue, by making choice of so unhealthy a place to live in, for their convenience being near the harbour. But the main oversight was to build their Town upon so unwholesome a place. For the ground being somewhat lower within the land than the Sea-baulks are, the Spring-tides flow over and there remaine, making a great part of that flat a kind of Bog or Morast, which vents out so loathsome a savour, as cannot but breed ill blood and is (no doubt) the occasion of much sickness to those that live there.

Labour had to be obtained for working the cane crops and the coffee, and for other agricultural industries. With very rare exceptions the emancipated negro would not work, he had no real desire even for property of his own—a plot of his own to till and sow. The negro peasant, in order that he may have enough to eat to-day, will work a little, but beyond that he is quite content and happy to lie in the sun. We shall have more to say later on the results of emancipation, for the abolition of slavery brought much evil as well as much good in its train.

Trollope, in his account of travels in the West Indies and the Spanish Main, thinks the reputed insalubrity of British Guiana, at all events of Demerara, to have been much exaggerated. Yellow fever he considered the only real danger and that, he says, is less of a menace than people at home believe.

There are many at home—in England—who believe that yellow fever rages every year in some part of these colonies and that half the white population of the towns is swept off by it every August.

It returns at intervals, but by no means regularly or annually. Sometimes it will hang on for sixteen or eighteen months at a time and then it will disappear for five or six years. Those seem to be most subject to it who have been out in the West Indies for a year or so, after that persons are not so liable to it. Sailors and men whose work keeps them about the sea-board wharves, seem to be in greatest

danger White soldiers also, when quartered in unhealthy places, have suffered greatly There are instances in which coloured people and even negroes have been attacked by yellow fever, but such cases are very rare Cholera is the negroes' scourge

Nor do I think this fever rages more furiously in Demerara than among the islands It has been very bad at Kingston, Jamaica, at Trinidad, at Barbados, among the shipping at St Thomas and nowhere worse than at Havana The true secret of its fatality I take to be this —that the medical world has not yet settled what is the proper mode of medical treatment There are still two systems, each directly opposed to the other, but in the West Indies they call them the French system and the English

Unfortunately Trollope does not give any details of either system, unfortunately also the remark still holds good Except for prophylactic measures "the medical world has not yet settled what is the proper mode of treatment"

Nearly thirty years after Trollope wrote the above a Demerara Conference took place (in 1888) to arrange for the adoption of a uniform system of quarantine That all was not at its best even sixty years after is evidenced by the resolutions passed at a West Indian Conference held there in 1922, dealing with malaria control, notification and segregation of lepers, sanitation public and personal (the appointment of a Sanitary Commissioner for the West Indies was recommended), infant welfare, training and registration and control of midwives, school medical inspection, vaccination of the people against smallpox and its milder form, alastrim

We must now turn our attention to another aspect of the subject, the manner of colonization and its effect upon the native population We shall see repeatedly in the sequel the dangers of contraction of infection by the colonists from the natives and the reverse of this Colonization may be carried out by settlers, by peaceful penetration, interfering as little as possible with the habits and customs of the natives, or by education, example and precept replacing some of their less commendable traits by better, or it may be by mere invasion and conquest—a selfish method without any regard to the benefit or future welfare of the native This last is naturally very disastrous and the evil may react upon the conquerors This hardly needs exemplifying, a reference or two will suffice Early in the eighteenth century the Hottentots were driven by the incursion of Dutch farmers from their fertile lands to the more barren districts to the north Many died from starvation and in 1713 an epidemic of smallpox broke out and killed many more The conquest of America is crowded with

analogous instances The Indians disappeared from Canada to the Argentine, and in the sixteenth century were largely confined to the Spanish-American colonies, the French and English had not at that time settled in America By the middle of the century the Indian had to a great extent disappeared from the West Indies and from much of the coastal and low-lying districts of Central and South America The literature of the Spanish Conquest teems with discussion of the causes of this Herrera attributed it to disease and he mentions in particular measles, smallpox, fevers and dysentery (bloody flux) Fray Motolinia, with greater candour, states that it was due to measles and smallpox in part, but also to war, famine and oppression Oviedo tells us that the native population of Santo Domingo (used for Haiti, but really the capital of the Dominican Republic on the South coast, founded by Bartholomew Columbus in 1496) at the time of the first Spanish settlement amounted to 'a million or more,' but by 1541 had been reduced to 500 He attributes this reduction of 99.95 per cent to pestilential smallpox which afflicted them "because God had repented of making such ugly, vile and sinful people"

The population of Peru is put as 10,000,000 at the time of the Conquest, in 1550 they were reduced to 8,000,000 and in less than two and a half centuries, in 1791, to 1,000,000 and a few thousand, undoubtedly owing to the invaders, for they themselves ascribe the depopulation to the hard conditions of life and to the influx of new diseases, in particular smallpox

It was the general belief, maintained by all the known writers of that time—Las Casas, Oviedo y Valdés, Herrera, Gomara, Cieza de Leon—that smallpox was unknown before the coming of the Spaniards We find confirmation of this in the records of its ravages in terrible epidemics among the Indians, whereas the Spaniards were spared In 1517 it raged in San Domingo and spread to Porto Rico, Cuba and other islands It was said to have been brought to Vera Cruz by an infected negro from Cuba in 1519 and to have spread through Mexico with devastating effects, causing the deaths of 'hundreds of thousands' Among the victims was the Aztec Cuiclahua, the successor of Montezuma, who had defeated the Spaniards and driven them from the capital

An even greater claim has been made for the assistance given to the Conquistadores by smallpox, it is a debatable point whether Cortez would have succeeded in the Conquest of Mexico without its aid, and the same applies to Pizarro and Peru, for Cieza de León records that 200,000 natives in Peru died of it

Smallpox was not the only morbidic adjuvant to the success

of the Spaniards Motolinia speaks of measles as one of Mexico's greatest afflictions He calls it *pequena lepra*—smallpox being *gran lepra*—and it caused a high mortality among the natives eleven years after the widespread outbreak of smallpox in 1519–20

Still more devastating was *tabardillo*, a form of typhus, from which also the Spaniards largely escaped By 1577 there had been six great epidemics and in the last of them, in 1576–7, according to Cieza de Leon, 2,000,000 perished Since then the disease has remained endemic

Thomas Hariot, writing of the Roanoke settlement, evidently has some compunctions and a feeling that the invaders were responsible, for he says

There was no town where they [the Indians] had practised any villainy against us, but within a few days after our departure they began to die In some towns twenty, in some forty, in some sixty and in one a hundred and twenty, which was very many in respect to their numbers

We must infer from this and other records that America before the Conquest was in general healthful

A subsequent chapter is concerned in some detail with the Slave Trade, we here, therefore, make but passing reference to it as the means of introducing disease and leading to the reduction of the native population Las Casas, writing of Hispaniola (*i.e.* Little Spain, the name given to Santo Domingo or Haiti), states that it was generally believed that the negro was stronger than the native Indian and the work of cultivation had to be done, the Spaniards would not and could not do it and they were loath to enslave the natives, so in 1501–03 the slave trade to this island began In 1522 many were brought to Cuba, one record states that 300 were landed from a single ship that year at Santiago, from 1530 onwards many were brought to Peru In 1763 the English took Cuba and were certainly not behind the Spaniards in slave-trade activity In seven months they introduced 10,700 negroes at 90 pesos a head Up to that time 60,000 had been sent to the island and in the next 27 years some 40,000 more

Slaves were introduced into New York in 1626, into New England in 1637, and into Louisiana before 1700 In 1799 the Portuguese were taking 70,000 annually from West Africa, and by that time the English, French, Dutch and Spanish were also competing Though a profitable trade the loss of life was enormous Vast numbers died on the march from the interior to the coast The average mortality on the voyage in the sixteenth, seventeenth and eighteenth centuries was over 30 per cent and occasionally

double or even treble this, from smallpox, fevers and dysentery. Slaves also carried malaria, yellow fever, leprosy, hookworm, filaria, yaws and, of course, syphilis and gonorrhœa, and some were suffering from trypanosomiasis, but this would not spread in the new country owing to the vector, the tsetse, being absent.

The question of the interchange of disease between the imported African slaves and the indigenous inhabitants is one of great interest. Some of it is still unsolved, part is in process of solution, for example yellow fever, by modern methods of immunity research. Speaking broadly, we may say that leprosy was probably brought by the slaves from Africa to America, later, but in far less amount, by other sources. Trachoma it is almost certain was another introduction, the ophthalmia which was very rife among the slaves was probably a mixture of trachoma, gonococcal and Koch-Weekes infections.

Scurvy, goitre and relapsing fever appear to have been present in America even before the coming of the white man, certainly before the introduction of slaves. Oroya fever, verruga peruviana (two forms of the one disease), piedra, pinta, chigoes were native to America. The last-named are said not to have been found in Africa until 1872, if that is so they were probably brought to Africa by the freed slaves who were repatriated and established in Liberia and Sierra Leone. The relapsing fever of America, though transmitted by a species of *Ornithodoros*, *O. venezuelensis*, *O. talag  *, does not produce cross-immunity with the African type transmitted by *O. moubata*, it is, therefore, improbable that the infection was brought from Africa to America. It is, of course, not impossible, the original African strain, not finding its customary host in the West, may have become habituated to the new species and then developed along a different line until the relations between it and its originator have become immunologically distinct. Relapsing fever is peculiar in this respect, in that the strain of a first relapse differs serologically from that of the primary attack, and that of the second relapse from that of the first, though usually reverting to that of the primary attack. The possibilities of this are obvious, the strain of a relapse being taken up by the local tick in America and breeding true *via* the tick, this, however, is pure speculation.

In brief, it may be said that the history of nations teaches us that extension of trade and intercourse between one country and another entails the possibility, almost the certainty, of diffusion of disease, the best example of which perhaps is yellow fever, brought to Martinique by the *Oriflamme*, to Grenada by the

Hankey, from the West to Spain again by the *Grand Turc*. Owing to her extensive and numerous colonial possessions Spain was the first country in Europe to be severely affected by yellow fever. We postpone for the present discussion of the interesting and much debated question whether yellow fever existed primarily in West Africa, America being infected from there, or whether it was present primarily in America.

The foregoing sketch, meagre though it is, may, we hope, serve to indicate the conditions under which men had to work in the early days of colonization, the foundations on which they had to build, the people they had to instruct, in whom medical men had to endeavour to instil the elements of hygiene and healthy living, and the diseases they had to combat.

Here, at the end of this brief account of the chief of the British colonies is a convenient place to say a few words on colonial medical development. The subject is a vast one and only the bare outlines will be touched upon. The question of the suitability of the tropics for the white man, or even the possibility of white colonization of the tropics as a permanent home for him and his descendants is beyond our scope.

Those who have studied the system of British colonial administration have again and again expressed surprise that a uniform plan is not adopted by way of simplifying matters. But, as Sir Anton Bertram has remarked in his book, *The Colonial Service*,

The signal feature of the system directed from the Colonial Office is not uniformity but variety. Starting in the days before the American Revolution with a simple and supple instrument of government in the Colonies and settlements of North America and the West Indies, it has developed and adapted itself to the most complex and diverse local conditions. Each local Government is a separate unit

as though the chief concern of the Colonial Office all through its history had been to foster local individuality,

and, later, "In small Colonies, as in great, those engaged in their administration are perpetually . . . upholding great traditions and doing large things, though it may be on a small scale."

This strikes the foreigner as peculiarly English. Johannes Stoye, a German, writing recently on the British Empire, observed

I regard the Empire as the outcome of the highly individual and not easily intelligible English character, which in turn is the outcome of the racial mixture, soil, climate and history that have gone to make England. Hence it follows that the Empire is as unsystematic and illogical as the Englishman himself.

The policy is really quite intelligible, it is a trusteeship for the well-being and development of people who are not able to look after their own affairs on coming into contact with the outside world—the development of the country “for the benefit of the inhabitants and the welfare of mankind” It is generally conceded, and it is in this that the success of the British as colonizers largely consists, that the interests of the natives must hold the first place and of these the medical view is a part Admittedly it was not always so Early colonizers went out for their own advantage by way of establishing trade, but even so they conferred benefits on the native, many of which have been permanent The Portuguese in colonizing Africa in the sixteenth century introduced the orange from China, India and Malacca, the lemon, lime and sugar-cane from the Mediterranean and the East Indies into São Thomé, Príncipe, the Congo and Angola, maize from Brazil, now found all over Africa, and many others—chilli (*Cap-sicum*), wheat, tobacco, pineapple, sweet potato, manioc (from which tapioca and cassava are made), rice, lentils, onions, guavas, jack-fruit, pawpaw, ginger—most of the things which constitute the diet of the native

Education on general lines we must leave aside, but the fact that the nature of this must depend on the stage of development of the race helps to account for the variety of it Nowadays it is understood that the education authorities should also be health authorities in teaching hygienic habits and safeguarding the health interests of their pupils, and so of the future generations The duty of medical men in the tropics—as at home—is to educate and so make the mass of the people participators in the knowledge of disease, its cause and prevention, with which they themselves, as men of science, are more fully acquainted In other words, the natives must be saved from themselves Tribal cultures will, it is true, to a great extent be destroyed by civilization, but the white man in doing his duty by the native inhabitants need neither displace nor exploit them Care for his nutrition will raise the native in health and physique, better housing and a higher standard of living will increase his respect for others as well as for himself The work of reformation is very difficult, but opposition on the part of the native is more often the result of ignorance than of wilfulness

Schemes for maternal and child welfare have now reached the stage that in some colonies the maternal and infant mortality rates may be not far below those in England, careful attention is given to the training of local nurses, midwives and health visitors

In Ceylon useful collaboration takes place between educational and medical departments, health visitors teach in the girls' schools and the older girls pay visits to welfare centres where they receive instruction in the care of infants. In Nigeria is a training centre for girls, they live in huts similar to, but a little better than, the village dwellings and a model hut is occupied by the older girls in turn while they fulfil their term as house-keeper to the community. Farmwork, cooking, marketing and care of infants are all subjects of instruction, the basis being the native methods but improved, though not beyond their capabilities of applying them in their own homes. There is no need to describe the courses in the different colonies—all that matters here is the principle. Exhibitions may be held, with 'model villages' and 'model buildings,' to show how things should be arranged. In Jamaica, for example, within the last quarter of a century or so there have developed some ten or more units of health activity, among which may be mentioned a Hookworm Commission, Commissions for malaria, yaws and tuberculosis, a School Hygiene unit, a Bureau of Health Education, a School for Sanitary Inspectors, facilities for the training of health workers and so on. Australia and Tasmania have their 'Bush Nurses' who do a wonderful amount of good and save the lives of many mothers and infants.

On a still larger scale, in many places malaria, yellow fever, cholera, enteric fever, and other diseases have decreased, in some they have even disappeared as the result of hygienic measures accompanying civilization—pipe-borne water-supplies, proper methods of disposal of rubbish and sewage, subsoil drainage and so forth, and elements of hygiene, health and cleanliness are taught to children as a regular part of the school curriculum, and to the older people by lectures, posters, health crusades and propaganda generally.

In modern times, as opposed to those of fifty or more years ago, the chief obstacle is not ignorance but finance. Sanitary improvements on a large scale are costly, while the demands on the small revenue of a struggling colony are many. Health is not a cheap commodity and the primary cost is but a part, there is the ever-recurring cost of upkeep which cannot be relegated to the future, and if a plant is not kept going, better were it had it never been begun, for the money has been wasted and might have been better spent.

In most tropical colonies it would be far too costly to employ more than a nucleus of Europeans on the medical and sanitary

staff To give one example, Nigeria has a population of 20,000,000, but the total strength of medical service is not above 100 European doctors, senior sanitary inspectors, nurses and health visitors are needed for administration, for special work, and above all for teaching the native With a large and scattered population local men, the best educated and educable among them, must receive training to relieve the European As Dr Chesterman has said, the difficulties are great and are not merely geographical The animistic belief is hard to combat, the native notices that we concern ourselves with the patient, he, as an animist, looks deeper into the cause—witch or devil This can be overcome only by proper training of subordinate staffs and their employment when trained The native's intellectual mentality in a vast majority of cases ceases to develop after puberty, his training, therefore, must be regulated by a minimum of theory and a maximum of experience A little knowledge (Pope's word was 'learning', he is usually misquoted in this) is a dangerous thing, but a lot of ignorance is even more dangerous

We have not space here to describe the various organizations directed to this end in those colonies which train the local men for medical work Such facilities are to be found in the Gold Coast, Nigeria, Uganda, Ceylon, Singapore, Fiji in the British colonies, and other nations, the French, the Dutch, the Spanish and the Portuguese also train the natives in their respective possessions to undertake medical, health and nursing duties

In 1928 the Union of South Africa appointed a committee to inquire into and report upon the training of natives in medicine and public health More than sixty witnesses were examined, many documents and memoranda were submitted and the report is important The subjects discussed were the problem of native health, a Government Medical Service, the advisability of providing for the training of natives in medicine and the nature of such training, the place and method of training and the certification of natives as medical practitioners, the same in public health and their certification as health assistants and nurse-midwives

The Committee recommended that

- 1 A Government Medical Service should be established incorporating existing mission hospitals
- 2 Better facilities should be provided for training natives as medical practitioners

- 3 The Service should be a full-time one and subject to regular inspection, so a 'qualified' native could not retire from the service and set up as a private practitioner
- 4 The standard of qualification should be the same as for that of Europeans

Other recommendations were for local application only and need not be specified. The committee suggested also the course of training which they considered sufficient for those desirous of becoming native health assistants.

To conclude this question we must record the developments to the present day of plans for research in tropical medicine. In 1933 a Conference of Governors of British East African Territories was held on the co-ordination of general medical research and another on 20th January, 1936, which considered also the question of veterinary research. Too often individual governors are averse to research on the grounds, or in the belief, that such is more academic than utilitarian. The conference discussed the appointment of a Standing Medical Research Committee and the facilitating of research while at the same time overlapping might be avoided. At this conference there attended members of the medical services of Kenya, Uganda, Tanganyika, Nyasaland, the Sudan, Zanzibar and the Belgian Congo. The programme put forward was a comprehensive one and included nutritional and metabolic problems, the dangers of transporting infected vectors of disease in aeroplanes, and among other conditions, of greater or less importance, certain problems of malaria, plague and yellow fever.

The question of the formation of a Colonial Medical Laboratory Service was also debated. The general idea was for each group of laboratories to have a director who would act in consultation with the respective directors of Medical and Sanitary Services and direct research to useful ends, that in such a service there would be officers engaged solely in research, others doing routine work with an assistant staff and laboratory personnel. By such means research would be unified and overlapping prevented. Under present conditions officers in different colonies, each already working at high pressure and often with inadequate staff, may be engaged on the same or closely allied problems. By the method proposed there would be organization and co-ordination and workers could be transferred from one district or laboratory to another whereby team-work could be undertaken in the laboratory and place best suited for a particular piece of research.

In 1936 also the Colonial Office, in consultation with the Medical Research Council, decided to establish a Tropical Medical Research Committee

to advise and assist in the direction of such investigations as the Council may be able to promote into problems of health and disease in tropical climates, and to make suggestions generally as to research in this field

This committee is a purely scientific body and includes representatives of the Colonial Office, of the London and Liverpool Schools of Tropical Medicine, and others who are experts in tropical medicine. The proposals included the establishment of a small staff of highly qualified men (or women) giving their whole time to research. To attain this, men with aptitude for research or young persons desirous of working in the tropics or on tropical problems are to be selected for Junior Fellowships which are tenable for three years. The first year is to be spent at a School of Tropical Medicine, the second in some research in such a school or other suitable institution, with a view to acquiring technique, and the third year is to be spent abroad on research work into some tropical problem. Some of these Fellows, it is hoped, will find permanent and pensionable appointments for research in tropical medicine. There are to be also Senior Fellowships either for those who have proved themselves as Junior Fellows or for others who have already had experience in research, at home or in the tropics. Apart from these special Fellowships the Medical Research Council are prepared to assist research in tropical medicine as opportunities arise.

CHAPTER IV

INDIA AND AUSTRALASIA

INDIA

It would be nothing short of presumption to attempt to describe in a few pages the condition of a country as large as Europe, excluding Russia, whose inhabitants differ widely in race, habits, customs and religion, and to trace the progress of sanitation there. In order to give some picture we can stop here and there to survey the restricted view as seen from milestones along the road. Later we shall give a brief account of the development and activities of what became subsequently the Indian Medical Service.

In the first half of the nineteenth century practically all that was undertaken was, on the one hand, an attempt by a few medical officers to improve conditions under which the British soldier lived and worked, and, on the other, more or less individual, at least local, efforts to obtain comfort and preserve health. So far as they themselves were not interfered with or inconvenienced, the generality of the people were allowed to continue as they had done for centuries. As Major Cunningham, Director of the King Institute, Gundy, Madras, wrote

The large mass of the people, living under the most primitive and insanitary surroundings afforded an almost unbounded field for the spread of every kind of epidemic disease. Fevers, smallpox, plague and cholera each took a terrible toll from the unfortunate inhabitants who frequently looked upon them as a sign of divine displeasure to be averted by prayers and sacrifices, rather than by precautionary measures. The exact mortality caused by these diseases will never be estimated. Contemporary literature, however, leaves no doubt of their severity. Of an epidemic of relapsing fever one reads that "of numerous native villages nearly the whole population was ill at one and the same moment" and "the banks of the river were covered with the dead and dying."

Between 1809 and 1811 a similar outbreak in Coimbatore and the district destroyed 100,000 persons and in 1818 a medical officer in the army of the Marquis of Hastings states that an epidemic, probably cholera, resulted in the death of 14,000 in

four weeks Such events awoke a feeling of fear, almost terror, in the mind of the white man and, as elsewhere, and even in England, fear and particularly fear of cholera proved a wonderful stimulus to sanitary reform, to better housing, disposal of refuse, and greater cleanliness generally

Between 1830 and 1846 the proportion of deaths ascribed to four diseases endemic in the Bombay Presidency, for every hundred Europeans serving there was Fevers, 23 0, dysentery and diarrhoea, 32 4, cholera, 10 3, hepatitis and hepatic abscess, 9 5 Probably the first real recognition of sanitation in the Army in India was an order from the Commander-in-Chief to the Senior Medical Officer in all cantonments to attend to the sanitation of them, this was in the year of the Mutiny

Here is an extract from a record by a municipal commission on the condition of Bombay in 1861

Go into the native town and around you you will see on all sides filth immeasurable and indescribable, and at places almost unfathomable, filthy animals, filthy habits, filthy streets, and with filthy courtyards around the dwellings of the poor, foul and loathsome trades, crowded houses, foul markets, foul meat and food, foul wells, tanks and swamps [the Commissioner's choice of adjectives appears to have been limited], foul smells at every turn, drains unventilated and sewers choked, and the garbage of an Oriental city Men, women, and children, the rich and the poor, living with animals of all kinds and vermin, seeing all this and inhaling the deadly atmosphere and dying by the thousand

In 1864 a Sanitary Act resulted in the formation of a Health Service, and in 1865 a Town Improvement Act was ratified and local boards were set up to appoint health officers and adopt measures for sanitation and supervision By 1868 there had been wrought a vast change

In three years [the Health Officer] has wrought a marvellous revolution Except in a few obscure lanes, the city is almost devoid of bad odours Its area is nearly thrice that of municipal Calcutta and yet every street and house and every road is daily swept as well as watered and the dust is carefully removed The natural effect has been seen, not merely in the comfort of all classes of the inhabitants, but in the fact that cholera, which used to be endemic in the city has not been known for some time

Let us pass on and obtain a glimpse of another capital town, Rajputana, about the same time

The poorer classes defile the outskirts of the town, the vacant spaces, old buildings and nearest highways, the rich inhabitants have places so much out of repair that the whole house and neighbourhood



JAMES JOHNSON
1777—1845



SIR JAMIS RANALD MARTIN
1793—1874



GEORGE MICHAEL JAMES GILES
1853—1916



SIR CHARLES PARDEY LUKIS
1857—1917

[Ivory blocks kindly lent by the Royal Society of Tropical Medicine and Hygiene]

reeks with foul odours from contaminated soil and masonry Drainage is very imperfect, and the sewage, deposited on low ground, becomes a hotbed of infection, whilst the wells and tanks in the vicinity are, of course, contaminated At the close of the rainy season houses and wells in low-lying situations have been frequently proved the starting points of serious epidemics Drainage from broken pipes saturates the walls of very many houses Bullocks and horses are stalled below rooms, and here the sick are also lodged Milch kine pick up a living in the streets and act as scavengers At night they live in filthy byres The litter from stables and cow-yards, if not eaten by the animals themselves, is turned over and over again till it rots The solid excreta of cattle are turned into fuel, the liquid saturates the earth so deeply that the wells are befouled, and the soil charged with saline matter Wells are usually situated in low places, while the general level of the surrounding soil has been raised by solid impurities and sweepings so much as to be, in some cases, many feet above the doorways of the houses Villages are very unhealthy after the wet season But they are swept by the life-giving winds which blow violently during many months of the year in Northern India

The ways of defiling water and food are innumerable On the margin of the village tank the dead are burned the buffaloes wallow in the mud, the sacred kine drink, the Brahmans wash their clothes and persons, and the women fill their waterpots The washing in water inconceivably filthy, merely as a symbolically religious act, the deposit of filth near wells and tanks, the religious obstacles to cleanliness, all contribute to mortal disease The women are employed for many hours every day in preparing with their hands animal manure as fuel, so it is impossible for the poor to have clean food Dogs, cows, swine, peafowl, kites and vultures do a large amount of scavenging

Since those days, of course, there has been great advance, but we are giving a picture of the time

Peshawar was once known as the graveyard of India, nor can this be a matter for wonder when we read what Dr Morton wrote in 1871 to the Sanitary Commission regarding the water supply for the city and the cantonments

No language could be too strong in describing the abomination of the whole existing arrangements Of course the grave and radical defect is the open main channel, exposed to every species of contamination The deeper channel is actually on a lower level than the ordure of the pits the effect on the unhappy dhooly-bearers may be learnt from the records at the station hospital, where in 1870 these poor creatures died like rotten sheep [whatever that may mean] In conclusion I can only say that I do not see how matters could be worse except in a community which drew no distinction between its cesspools and water-tanks, and used each indiscriminately for all purposes

The water-tanks were certainly a most dangerous source of infection in most Indian towns and the wells in villages Thus,

the tank within the great temple of Madura has been for hundreds of years used by the people as a bathing-place before presenting their offerings to their deity and on an average 200 bathe and wash their clothes there every day as a sacred duty (*Report of the Sanitary Commission with the Government of India, 1871*) How difficult it is to bring home to the ignorant and the superstitious the danger of insanitary practices is seen when we read that years later, in 1888, Mr Justice Cunningham wrote

The tank is often mere sewage Every shower washes surface filth into it, every dust-storm carries some more, a perpetual series of bathers adds daily to its impurity, clothes and cooking utensils add their modicum of dirt, as the dry season lasts it grows dirtier and dirtier

One more picture, this time of the town of Cumbum as reported upon in 1875 by the Sanitary Commissioner of Madras

The chief predisposing causes of the abnormal sickness and mortality of the town were the crowding of every available spot within its limits with corpses, and pollution of its water supply The exciting cause is malaria arising from a swamp which, owing to partial silting up of an important irrigation channel, has replaced for about two miles the running stream which originally drained efficiently the irrigated lands More tombs than living persons are visible in the town The borders of wells and water-channels seem chosen especially for sepulture

The usual mode of obtaining domestic supplies of water was for the *bhisti*, with his shoes on and regardless of the filth that has accumulated on them, to step into the reservoir till the water reached his knees and then fill his receptacle by immersion

At the various villages the wells were surface wells, in some villages where cholera was present the water was only 3 to 4 feet from the surface and more or less surrounded by *ghuls* which had overflowed and added their impure quota, water fouled by human excrement and filth, to the well Moreover, the wells were often close to the cesspools

As the improvement of the water-supply in England was largely instrumental in preventing cholera epidemics, so has it effected the same in parts of India, Calcutta for example The epidemic of 1849 in England and Wales caused 53,293 deaths, that of 1854 caused 20,097, that of 1866 14,378, since which time cholera can be said not to have succeeded in establishing itself at all Similarly, after 1870 when a good water supply was introduced into Calcutta, a marked improvement set in in the health of the city and in the cholera returns An even more instructive example—more instructive because the result is more easily seen—is that of the

village of Puthian Puttur in the Tinnevely district This had been reported in 1870 as "exempt from cholera, cause unknown" A missionary, a Mr Kearnes, residing in the village, wrote that when he came to live there few villages suffered more from cholera and fever There were filthy channels and foul water draining from the surface soil into the wells, the native houses had disgusting yards, the cholera mortality was very high With the aid of the local officers, Mr Kearnes set about improving the place The wells were all walled up above ground-level, the channels improved and their contents deviated to the land Pools were filled in and precautions taken to drain waste water away from the mouths of the wells A system of cleansing was organized and the people prevailed upon to take an interest in their own health and that of the community He concludes, "hence there is now no cholera"

The massing of people at great fairs, like those of India, for pilgrimages like those of Mecca, has contributed very largely to the origin, and the disposition, habits and customs of the people to the spread of cholera mainly, but of other diseases also, in Asia and Europe

The pilgrimages at Mecca have their counterpart in India at Hardwar (see the chapter on Cholera), Ajodhya, Bindhyachal, Gola Gokarannath, Garhwal, Piran Kahar and elsewhere At Hardwar, previous to celebration of the rites each pilgrim, standing at the side of the well, has a bucket of water poured over him and he drinks as much of the water as he can, that poured over him passing back into the well In describing the pilgrimage of Mecca in 1865, in a paper read before the Sanitary Institute, Mr Christie states

Within six days after these ablutions and the drinking of the water of the Zem-Zem, the streets of Mecca and its mosques, the twelve miles of road lying between the city and Mount Arafat, were cumbered with the dead

The beginning of steady improvement in the sanitation and health conditions may be said to date from the Sanitary Act of 1864 and that of 1866 directed to the conservancy of cantonments By 1867 forty-four municipalities had been constituted and registration of births and deaths introduced Vaccinators were appointed, and a Sanitary Commissioner with the Government of India whose duties were subsequently merged with those of Director-General of the Indian Medical Service (see below) Calcutta and Bombay appointed special health officers and civil surgeons were

made municipal advisers on health matters. In the Madras Presidency they became District Medical and Sanitary Officers, each with an assistant surgeon to carry out defined sanitary duties. In 1888 sanitary boards were formed in each province, but rural sanitation lagged and does still lag far behind that of towns. In 1899 Madras University instituted a Public Health qualification open to medical men.

The generality of the people were unprepared for reform and were suspicious of western measures when attempts were made to introduce them into eastern ways. The Health Officer for Calcutta recognizing this fact, submitted to the Medical Congress in 1894 a scheme for an organized sanitary service for India. This was approved and its adoption was recommended to the Government, but was held over or forgotten when in 1896 plague entered at Bombay and invaded a large part of the country. This epidemic did not turn out to be an unmixed evil, for the Plague Commission of 1898 stimulated sanitary action and since 1902, when the King Institute for Research was founded at Guindy, several laboratories have been established and an important Journal of Medical Research issued, owing largely to the instigation and support of Sir Pardey Lukis, then Director-General of the Indian Medical Service.

In 1906 the post of Government Sanitary Commissioner was revived, but five years later his duties were amalgamated with those of Director-General. A regrettable arrangement was made in 1911, by which, for some reason difficult to fathom, sanitary matters were placed under the Education Department. During the next decade or so the sanitation officers underwent as many changes in nomenclature as a film star, or zoological specimen. The Sanitary Commissioner, without change of duties, became a Public Health Commissioner whose duties were largely advisory. Sanitary Commissioners in Madras, Bombay, Burma, the Central Provinces, United Provinces, Assam, in short the Provinces in general, became Directors of Public Health, still with duties mainly advisory, but having under them sanitary inspectors and vaccinating staffs.

The municipalities of most large towns now have their own Medical Officers of Health with subsidiary sanitary staffs.

In 1923 certain changes were effected which included the creation of a Central Imperial Board of Health with advisory functions, establishment of an Epidemiological Statistical Office, conversion of the Sanitary Commissioner into a Public Health Commissioner and his deputy into a Director of Medical Research,

for provincial needs Departments of Public Health were founded, Sanitary Commissioners and their deputies became respectively Directors and Assistant Directors of Public Health

One of the greatest difficulties, perhaps from an administrative point of view the greatest of all, in setting up an Imperial Sanitary Service is that, with so much variation of language, habits and religions as exist in India, transfer of an official from one part to another would be unworkable

When all is said and done, the most fruitful means of promoting public health among native races consists in education and actual demonstration, and that the Government of the United Provinces was fully alive to this is shown by the following which appeared in the *Indian Medical Gazette*, August 1922 :

The Government of the United Provinces has instituted a Hygiene Publicity Bureau and has commenced a Hygiene Publicity Campaign. It has long been felt that steps must be taken to familiarize the general public with the knowledge of how to protect themselves against epidemic diseases, and that no general advance in public health can be attained until people are educated in rural and municipal hygiene and are prepared to bear the expense of hygienic and anti-epidemic measures. The publicity scheme consists of popular lectures, magic-lantern demonstrations and the distribution of illustrated booklets and posters. Small, well-written, concise and well-illustrated booklets on such subjects as cholera, plague, malaria, tuberculosis, smallpox, etc., have been prepared in English, Urdu and Hindi. Twenty-five sets of lantern-slides have been prepared in connection with each subject, and twenty-five sub-assistant surgeons in charge of travelling dispensaries have been trained in publicity work and posted to the more unhealthy districts.

As funds become available it is intended to provide materials for a hundred lecturers and to produce further booklets and pamphlets dealing with relapsing fever, ankylostomiasis, water and food supplies, village sanitation, etc. Also to provide travelling hygiene exhibitions, establish hygiene museums, and to provide health visitors and midwives.

The whole United Provinces scheme is admirably thought out and well organized. Only when there has been created an intelligent public opinion and a popular demand for improved hygiene will it be possible to obtain the funds necessary for real improvement of the conditions of rural hygiene in India.

The present organization may be summed up as follows. The Public Health Commissioner with the Government of India is the Government's adviser on all public health matters, gives advice when asked by local governments and provincial Directors of Public Health, and corresponds with the latter direct on technical subjects. He is in administrative control, acting on behalf of the Director-General, of the Medical Research Department and is Secretary of the Scientific Advisory Board and of the Governing

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Body of the India Research Fund Association For years he has been a member of the Health Committee of the League of Nations and a member of the Advisory Council of the League of Nations Eastern Bureau (Singapore), and is the delegate for India to the Office International, Paris

The Medical Research Department has a cadre of thirty posts, four at present (1937) in abeyance Of the twenty-six remaining eighteen are reserved for officers of the Indian Medical Service There are specified appointments, which are the posts of Directors and Assistant Directors of the Central Research Institute, Kasauli , of the Haffkine Institute, Bombay , of the King Institute of Preventive Medicine, Madras, and several of the Pasteur Institutes The first of the above-named institutes, that at Kasauli, is the only laboratory directly under the control of the Central Government It is directed by the senior officer of the Medical Research Department who is Editor of the *Indian Journal of Medical Research* , there are three Assistant Directors, and working there are officers engaged on special investigations Here are prepared prophylactic vaccines, typhoid and paratyphoid, cholera, etc (but not plague), and snake antivenenes for the whole of India , in addition the usual work of a routine character such as is performed at any large laboratory is carried out

The Indian Research Fund Association maintains an organization for the Malaria Survey of India and another of laboratories for Nutritional Research The former is under the charge of a Director, with an Assistant Director (both experienced malariologists), a malaria engineer, an entomologist, a biochemist, and other assistants Its functions are - (1) To advise the Government on all issues relative to malaria in India , (2) To initiate investigations in malaria , (3) To undertake systematic research and make the results available for practical application , (4) To carry out epidemiological investigations , (5) To advise and assist in carrying out anti-malaria measures , (6) To undertake clinical work , (7) To train officers and others in practical malaria work , and (8) To publish scientific results

Prior to 1920 Indian medical graduates were accustomed to come to Europe for post-graduate courses in tropical medicine and hygiene In 1914 Sir Leonard Rogers proposed the establishment of School of Tropical Medicine in Calcutta and an Institute of Hygiene in Bombay, each on an all-India basis In spite of a certain amount of opposition Rogers carried his project through, with the help of the Government of India, the Government of

Bengal and private supporters, and in 1920 the Calcutta School of Tropical Medicine and Hygiene was opened with a highly qualified teaching and research staff whose work has brought untold benefit to the whole tropical world. Beside the school proper it comprises the Carmichael Hospital for Tropical Diseases with an out-patient department. The Faculty of Tropical Medicine and Hygiene, Bengal, grants a diploma after examination to those who have completed the course at the school. Mere enumeration of the subjects of research already undertaken will show the multifarious nature of the work done. Leprosy, anæmia, helminthology, bowel diseases, malaria, synthetic drugs, indigenous drugs, cholera, kala azar, epidemic dropsy, medical mycology, diabetes and others.

The Nutrition Research Department also covers a wide field and undertakes diet surveys, studies malnutrition and deficiency diseases, analyses and determines the nutritive value of native foods and so forth.

In the foregoing an attempt has been made to sketch chronologically the sequence of events and the development of sanitary administration in India. We will now retrace our steps in order to give an account of the rise and development of the Indian Medical Service. For what follows I am indebted to the work of Colonel Crawford, the well-known historian of the service.

From the earliest days of the East India Company a Marine Medical Service was provided for the medical requirements of the company's ships and personnel. The status of the medical officer in those days was not an exalted one. Mention has been made elsewhere of the complaint of a medical officer of his being beaten with a cutlass by the captain, of being keel-hauled, and other forms of ill-treatment, and of another who was kept three weeks in irons for whistling on the quarter-deck.

The company maintained a hospital at Madras from 1664 and twelve years later another was established at Bombay, to which much benefit was attributed, for in a letter written in the following January we find these words:

Whereas last year from October to February there died above a hundred men, this year we have not lost fifteen, most of w^{ch} of imposthumation in y^e liver, much of w^{ch} benefit wee must attribute to o^r new hospitall. for the souldiers do not die by any such fatahty concomitant to y^e clime as some vainly imagine, but by there [*sic*] irregularity and want of due attendance when sick. For to persons in a flux w^{ch} is y^e country disease, strong drink and flesh is mortall, w^{ch} to make an English souldier leave of is almost as difficult as to make him divest his nature, nay though present death be laid down

before him as the reward of y^e ill gratifying his palate This is the true cause our Bombay bills of Mortality have swelled so high, whereas in y^e Hospitall nothing can come in or out wthout passing y^e Doctours eyes

In 1707-8 a third hospital was built in Calcutta In 1715 or thereabouts another new development, female nursing in hospitals, was adopted in Bombay A Mrs Peck was sent from England to take the post of matron to the Bombay Hospital, soon afterwards she married the company's Master-Carpenter, but history says nothing about her resigning her position as matron We do not know of what materials the Calcutta hospital was constructed, but it did not last very well and by 1754 was sadly in need of repair The surveyors reported

The Door Frames and Windows are almost all so bad that they must be changed, the South West and West part of the Hospitall especially that were [*sic*] the lightning struck it is so very bad that Borgues (small crossbeams) having given way and the Beams and Burgers gone that if new Buttresses is [*sic*] not speedily put that part will fall down The Westerly wall has belled out two feet there is an absolute Necessity to buttress immediately to keep the Wall standing, the North East End of the Hospitall is crack'd in number of Places and the Arches given way so that part likewise must be buttress'd to keep it from falling The whole Hospitall must be speedily whitewash'd and Plaistered as should the Rains get into the Walls it will carry away all the mud from between the Bricks and in Danger of the Whole

Neither the composition nor the spelling of the surveyor is above reproach, but it is clear that the building was in a parlous state

The pay of the company's medical officers in the early days was very low and their duties multifarious Thus, the Surgeon-General received a remuneration of £20-£30 a year and in addition to attending daily

from morning until night, to cure any persons who may be hurt in the service of this Company, and the like in all their ships they shall also cut the hayre of the carpenters, saylors, caulkers, labourers and any other workemen in the Companies said yards and ships, once every forty days, in a seemly manner

Later, till January 1764, medical officers received £36 a year in Bengal and Madras, rather more in Bombay In those days, we are told, a physician held a position superior to that of a surgeon or apothecary Many, of course, are of the same opinion to-day

The Bengal Medical Service was founded by orders dated 20th October, 1763, and became the Indian Medical Service in the

succeeding January The question is commonly asked whether the Indian Medical Service is primarily military or civil In 1766 and again thirty years later it comprised or was divided into two separate services, but on each occasion the arrangement was found impracticable and they were united The question has been finally settled that officers of the Indian Medical Services are all primarily military officers, that those in civil employ are lent temporarily only for civil duty, that these form a reserve for the Army and that they are liable to recall to military duty at any time

The East India Company, in addition to the Indian Medical Service, maintained four other medical services, namely, the St Helena, the West Coast of Sumatra, Prince of Wales Island, and the China medical services

The Government of India was transferred from the company to the Crown in 1858

For a century past medical education has been carried on in India at several places In 1835 a Medical College was established in Calcutta, and between 1837 and 1912 ten professorial chairs were instituted, nine between 1857 and 1871 Madras Medical College was first established as a Medical School in 1835, and the Grant Medical College, Bombay, was opened in 1845 There are several vernacular medical schools for training hospital assistants, in Bombay there was one established at Poona in 1878, one at Ahmedabad in 1879, and a third at Haiderabad (Sind) in 1881 By 1912 there were medical schools established in Northern India at Agra (opened in 1853), Lahore (1860), Scalda, Calcutta (1873), Patna (1874), Dakka (1875), Cuttack (1876), Indore (1878), Ludhiana (1895), Rangoon (1907) and Lucknow (1912)

Mention has already been made of the Government of India despatch with detailed proposals for the appointment of Sanitary Commissioners In accordance with this despatch one was appointed for each of the five chief provinces Bengal, North-West Provinces, Punjab, Madras and Bombay, and the then existing Sanitary Commissioner of the first of these became Sanitary Commissioner with the Government of India

Medical education at home for those intending to serve in India was undertaken from 1860 at the Army Medical School at Fort Pitt, Chatham The Royal Victoria Hospital, Netley, as well as the school at Fort Pitt owe their foundation to the Crimean War The foundation stone of the Netley Hospital was laid by Her Majesty, Queen Victoria, on 19th May, 1856, the building being completed and opened in 1863 In the earlier days Netley

was also the training school for medical officers of the Royal Navy, until Haslar was opened in 1880

At the beginning of the present century, in 1901, the Royal Army Medical College was established at Millbank. Army medical officers did not receive their instruction at Netley after June 1902, but those of the Indian Medical Service continued to do so for another three years, since then both are trained at the Royal Army Medical College and at Aldershot. It is a debatable question whether it would not be better for officers entering the Indian Medical Service to get their instruction in India, for there is abundant material for clinical study and for research there, and thus in the country where their life-work will be performed

AUSTRALIA ¹

Within the past hundred years Australia has passed in a rapid, compressed form, as it were, through experiences to which England was subjected during several centuries. Just 100 years ago a letter appeared in the *Lancet* with the title, which might have been more happily expressed, unless intentionally ambiguous, *Uselessness of Medical Men in Australia*. The writer says

Having recently returned from Australia, where I was persuaded to go as the surgeon of a ship under the assurance of there being a great demand there for medical men, I permit me to put young men on their guard against such an impudent imposition. The climate is the finest in the world, there is abundance of everything at a cheap rate, plenty of employment, and the labour is well paid. Raiment and fuel are almost not needed, they have there neither endemics nor epidemics, and the consequence of all this is Health of the Highest Order.

The following year another letter to the *Lancet* confirmed this

Mr Wyatt, an English surgeon, formerly in Plymouth, who became a magistrate in Australia, states that he has not found any patients in Australia, either to claim his own attention or that of any townsman who may be qualified to practise medicine.

Not long after, however, settlers crowded into towns, towns became cities, and these were soon rendered insanitary and, despite the climate, disease was introduced and found conditions favourable to their spread. From the hygienic point of view, matters had been allowed to get into a parlous state and in 1888 the Lecturer in Hygiene, University of Melbourne, Dr Springthorpe,

¹ Much of what follows is taken from a previous work by Sir Andrew Balfour and the author on *Health Problems of the Empire*, London, Collins & Co., 1924.

wrote regarding Victoria, that there was never any attempt at town cleansing, footpaths were untidy and at night the odours in the side streets were those of badly kept cesspools

Round the corner of the imposing Town Hall meanders a rivulet laden with foul odour—it has smelt just the same for some years. It would be interesting indeed to know, in acres, the total area of filth in and around Melbourne, in the shape of dirty rights of way, neglected dustbins, sodden manure heaps, made ground polluted in diverse ways, soil pans in use, or empty but dirty, road sweeping, cinder and rubbish heaps, stagnant foetid drains and the like. And, to crown all, we have converted our beautiful waterway, the Yarra, into a magnified, obnoxious open sewer.

In parts of Victoria, however, the gold rush of the middle years of Queen Victoria's reign brought many immigrants from the home country, health conscious after the cholera outbreaks of their early days, and there matters hygienic were in a better state. The adjoining State of New South Wales on the contrary remained in its primitive condition except for minor laws regarding nuisances and local health regulations on the coast. In 1881 there was a serious outbreak of smallpox in Sydney and the fatality rate was high, 26 per cent. The only official with power to take steps was an old practitioner, the port medical officer who was also in charge of the quarantine station and a hospital hulk to which male patients might be sent. A board of advice—five medical men and three executive officials—was constituted. An ambulance service was started, houses were quarantined and patients removed to the quarantine station in the port. The epidemic declined after seven months and an Infectious Diseases Supervision Act was passed by which a Board of Health was formed. A Commission was appointed to investigate the late epidemic and the quarantine conditions were shown to be in a bad way. As a result of their deliberations a small coast hospital and a sanatorium were erected and abundantly justified itself in the influenza pandemic of 1919. At the present time this has grown into a modern institution with 750 beds for infectious, medical or surgical cases and is situated in a beautiful position.

We said above that the experiences of Australia in the past century were a sort of rapid review of those of England during several hundred years. To quote what we have written elsewhere on London and the large towns of England in the sixteenth century

The sanitary arrangements were not only crude but dangerous. Only the fortunate, the hardy, or those who, owing to mild attacks of disease or the frequent absorption of small doses of virus, had acquired

immunity, survived the perils to which they were exposed. The infant mortality was huge, the death rate high, the expectation of life exceedingly uncertain. It was an age of filth, of public and personal filth. Water supplies were easily fouled. The houses were often dirty, the streets, as a rule, woefully unclean. The town was for the most part a mere huddle of dwellings, overcrowding was rife and determined efforts had been made thus early to exclude sun, and light, and air. Vermin of all kinds abounded. It was a foul age and the Great Fire of London had not yet come as a purifying agent. Away back in 1287 a law had been passed for London making every householder responsible for cleaning the street in front of his own premises. Those who had no land wherein to bury refuse and excreta, and who, owing to the houses being built of wood and to the lack of fuel, dared not burn it, found the Thames [or the Fleet, or the ditches round the walls] a useful cloaca. Into it was thrown all the dung and garbage until it was in danger of being blocked!

In Edward III's reign a law was enacted forbidding this fouling of streams and ditches and enforcing removal of rubbish by carts to places outside the city, the practice persisted, however, as no communal action was taken.

To return to Victoria, Australia. There was no properly-designed system of drainage, subsoil drainage was a thing unknown, housing consisted of closely packed tenements, without drainage, insufficiently ventilated and damp from rising moisture. Filth began to accumulate around these dwellings. Parliament passed an Amending Health Bill, but, as so often with legislature sound in intention, rendered the whole nugatory by striking out the clauses which gave the Sanitary Authority a controlling power in these matters. Enteric fever raged, in the six months, December 1888-May 1889, there were 5159 cases reported to the Central Board of Health, and 789 of them were fatal.

New South Wales (see above) was said at the time to be as bad and one delegate to the International Medical Congress of Australasia which took place in 1888-9 stated the needs were three: special legislation, organization and co-ordination of authority, and the sympathy and assistance of the public. It may be mentioned here that Australia now has all three.

Since the early 'eighties the relationship between the Federal and Local Health Administrations has been much more close. Federal Quarantine Stations were established at Albany and Thursday Island in 1884. A Second Australasian Congress was held in 1896 and consideration was then given to uniformity of quarantine administration. Four years later a third conference, known as the Intercolonial Plague Conference, was concerned with plague which had reached the country. The Fourth Con-

ference of 1904 led to the Quarantine Act of four years later, the fifth in 1905 discussed the draft regulations and details of administrative practice. In 1912, 1915 and 1920 the Quarantine Act of 1908 was subjected to amendments. The Director of Quarantine became the Commonwealth Director-General of Health and permanent head of the department, the bulletins which the department issues regularly show that it now has an excellent organization. The results afford further and corroborative evidence of this. The death rate for the Commonwealth fell in 1920 to 10.6, that for England and Wales being 12.1, the infant mortality rate had been reduced by 50 per cent, deaths from enteric fever in 1890-9 in Victoria had been 33 per 100,000 inhabitants, in 1920 only 3.7, while in the Melbourne Metropolitan district the rate fell from 43.56 to 1.7 in the same period.

NEW ZEALAND

The history of sanitation in New Zealand in the earlier days is in the main a replica of that of Australia. Towns were laid out—one can hardly say planned—and built without any proper provision for water-supply or sewerage. No real sanitary inspection preceded the erection of public buildings, no supervision was exercised. It indeed appeared as if history would repeat itself and that “no awakening would take place until a succession of dire epidemics decimated and horrified a repentant and alarmed people.” Infective diseases were prevalent in Wellington, which was in those days far different from the model town it has since become, Dunedin had many infected patients but no provision for dealing with them, Napier was a badly drained swamp.

Improvement may be dated from 1900 when a Public Health Act was passed and New Zealand created the first Minister of Public Health. Fear has repeatedly provided the stimulus for a town or country to bestir itself and set its house in order, and this was no exception to the rule, but it was not, as often elsewhere, cholera but the fear of introduction of plague from Australia.

In 1912 the New Zealand University granted a diploma in public health. After the pandemic of influenza of 1918-19, a third Act (in 1920) repealed the Consolidated Public Health Act of 1908 with its amendments and the broad and comprehensive administration of the present Department of Health was inaugurated. There was appointed a Director-General with a deputy and several divisions under him, of Public Hygiene, Hospitals, Nursing, Dental Hygiene, Child Welfare and others, each with

its own director The Dominion is divided into Health Districts, each with its Medical Officer of Health, and there is a Health Board of which the Minister of Health is Chairman Thenceforward New Zealand has led the world in its low infant mortality rate, in 1919 it was only 45·3 per thousand births, when that of England and Wales was 89, or practically double

CHAPTER V

MALARIA

1 INTRODUCTORY DISTRIBUTION

There will be a general agreement among those who have studied the question of disease in warm climates that malaria is of the utmost importance. This opinion will be based on several grounds. The imperialist will say that it has proved the greatest hindrance to successful colonization, that it has been the ruin of many a carefully planned expedition, the statistician will show that it is the most potent single cause of sickness, invalidism and death, the clinician will point to its protean manifestations, to the difficulties in diagnosis, to the failure to cure in many cases, the hygienist will express wonder that in spite of all the knowledge of the causative parasite, of the mode of its transmission, of the habits of the vector, the results of application of this knowledge have on the whole been disappointing.

The story of malaria is many-sided. Volumes would be needed to give anything like an adequate account of its varied intensity of prevalence in different parts of the globe, of its change in distribution within historical times, of the mischief it has wrought, of the developments it has hindered, the schemes it has thwarted, the reputations it has ruined. The story of the gradual elucidation of the cause, the transmission, the possible means of prevention and the application of them is another side full of interest, the story of Cinchona is replete with romance, the attempts to find satisfactory substitutes when there were possibilities of the supply failing, the manufacture of synthetic chemical substances for treatment constitute an aspect of the highest interest to the clinician.

Though we are inclined to regard malaria as a disease of warm climates, we do so merely because it inflicts its greatest damage there, not because its ravages are limited to them. It is far from uncommon on the Continent, it occurs in Russia, in the United States and was once frequently met with in England, in

fact this country of ours is not yet quite free from it. Though now unknown as an indigenous disease in Scotland, Ireland and Wales, it still lingers in the Fens and in the district of Romney Marsh. Its existence in the Essex and Kent marshes was common knowledge in the days of Charles Dickens. The following occurs in *Great Expectations* in the conversation between Pip and the convict. Pip says "I think you have got ague"—"I am much of your opinion, boy," said he. "It's bad about here," I told him. "You've been lying out on the meshes, and they're dreadful aguish."

We speak nowadays of malaria as if it were one disease, our predecessors spoke of marsh fevers, in the plural. They did so purely on clinical grounds, including under the term · intermittent fever—tertian, quartan, and quotidian—marsh remittent fever, Bengal fever, Jungle fever, Hill fever, Teraí fever at the bases of the mountain ridges, bilious remittent fever. Putrid remittent marsh fever was a term used for malaria with the probable addition of some scorbutic taint, for it was common on landing in a malarious country after a long voyage with overcrowding and improper food. Hirsch states that Rocky Mountain fever now known to be a *Rickettsia* allied to typhus and tick-borne, was a synonym of malaria, an indication of how ill-defined malaria was even in his day.

The acumen of practising physicians of seventy or more years ago, before the parasite of malaria was discovered, is manifested in the fact that, though they knew of tertian and quartan fevers and of quotidian intermittents and were puzzled by the occurrence of pernicious forms in which special symptoms might predominate, such as coma resembling that of apoplexy, convulsions like those of epilepsy, pulmonary symptoms leading to confusion with pneumonia, intense diarrhoea recalling dysentery or even cholera, vomiting like that of acute gastritis, nevertheless they were not looked upon as different diseases, but as different manifestations of malaria. Trousseau even differentiates clinically the quotidian fever such as occurs in malignant malaria from that due to double (benign) tertian or triple quartan. He noticed that in true quotidian the paroxysms were closely alike, whereas in double tertian the third day attack resembled the first and the fourth the second, whereas the first and second did not resemble each other, similarly in triple quartan the fourth and first, the fifth and second, and the sixth and third day fevers respectively resembled one another. Trousseau speaks of the analogy of malaria with a diathesis, such, for example, as gout, because the disease will break out again and again after intervals

without any fresh infection and because it may be latent for varying periods. In spite of this latency—Trousseau quotes instances of persons contracting infection abroad, but not showing symptoms till arriving home and so making it difficult to connect cause with effect—the medical men of the day were not often deceived. They knew also that the ‘paludal diathesis’ was exhibited, not always by attacks of fever, but also by anæmia and cachexia, they apparently believed in congenital transmission of the infection or, at least, of the diathesis, for Trousseau mentions that he had observed in Sologne children born with visceral enlargements, large spleens and cachexia of the skin “testifying that even in the womb they had been under the same evil influence as that in which their mothers had lived.” He was thoroughly familiar with the manifestations of congenital syphilis and as he makes no mention of the latter in this connection we must take it that he did not regard syphilis as responsible for the condition.

There were, of course, exceptions among the doctors of the day who doubted the unity of the cause. As Hirsch states

So long as we remain ignorant of the nature of the malarial poison we shall be working merely on a basis of probabilities in attempting to answer the question whether there are various morbid poisons underlying the various forms of malarial disease or whether there is only one malarial poison whose kind of effect is various according to the quantity in which it acts and according to the predisposition of the individual affected by it.

In favour of the latter is the fact that in epidemics and even in the same person one may observe transmissions from one form to another, or different forms at different times. Rana'd Martin noted that many patients give a history of suffering at first from remittent (Jungle) fever and later from the intermittent form (Sydenham, it will be remembered, noted a like sequence and we see it also to-day in some cases of malaria inoculated for therapeutic purposes). Elsewhere, however, Martin's description seems rather to indicate that his ‘remittent fever’ is malignant tertian infection and ‘intermittent’ is benign tertian and quartan.

Bryson, whom we referred to when speaking of the Navy, in his statistical report on the health of the Navy in the East Indies, speaks also of the fever of China and says

A large proportion of, or nearly all the cases of, intermittent were the sequelæ of fevers which had first appeared in the continued or remitting forms, still there were a few which seem to have been intermittent from the commencement, although it is probable they were connected with preceding attacks which were not observed or had been forgotten.

The very name 'Malaria,' sanctioned by long usage, is a perpetuation of error, for it has no connection with 'bad air' as such Sir John Forbes and Sir Ranald Martin recognized this nearly a century ago, when the latter, quoting Forbes, wrote

Neither impure air simply, nor wet, nor the alternations of cold and heat, nor all these combined, can give rise to fevers of this type
And he adds

This, I believe, to be quite true in regard to a *first seizure*, but *after that*, and when the disposition to relapse is once established in the system, such a combination of influences will certainly, in tropical climates, prove an efficient cause

At the same time instances are on record in which in pre-mosquito days the bad air seemed to be the direct cause Trousseau reports carriage of infection by air currents to a considerable distance He mentions that a party of thirty were walking towards the mouth of the Tiber, when a wind from the marshes met them and all but one suffered from fever This instance is also mentioned by Lancisi, but nothing is said concerning any interval for incubation after infection and it is doubtful whether, if the usual eleven days or so had elapsed, the connection with the walk would have been noticed, and on the other hand the members of the party were inhabitants of Rome where they would have abundant chances of becoming infected, when a chilling from meeting a wind blowing from the Tiber might easily induce a recrudescence

We have tried to discover who first used the term 'malaria' and when If we consult the more modern textbooks we find it stated that the name was given by Francisco Torti in 1753 in his work *Therapeutica specialis ad Febres periodicas perniciosas*, written in Latin Hackett in his Heath Clark lectures says the name was "introduced anonymously in 1793", he gives no authority—"anonymously" does not help much and the date is probably wrong Boyd in his *Introduction to Malariology* states that the Italian word 'malaria' was first introduced into the English language by Macculloch in 1827 Macculloch says "This is the unseen and still unknown poison to which Italy applies the term that I have borrowed, Malaria" He certainly was not the first to use the term in English, for, according to the *Oxford English Dictionary*, Horace Walpole in 1740 wrote "A horrid thing called the mal'aria, that comes to Rome every summer and kills one" Charlotte Smith in 1801 and J Forsyth in 1813 both used the word before Macculloch The others are wrong also, for there

was no edition of Torti's work published in 1753. Torti was born in 1658 and died in 1741, at the age of eighty-three. His book was first published, not in 1753, but in 1712, and editions appeared subsequently in 1730, 1732, 1743 and 1755. The work is full of interest, but we have searched through it and read much of it but have failed to find the word 'malaria'.

Again, in Celli's *History of Malaria in the Roman Campagna* there is a reference to a publication by P. F. Jacquier, entitled *Sur la malaria (sic) et les maladies qui apparaissent sur d'autres plages d'Italie en été*, Rome, 1743. This I have not been able to see, but if true it antedates the reputed year of the textbooks by a decade, though not the use of the word by Walpole. On the other hand, the quotation of Walpole does not necessarily mean something that was regarded as a distinct disease. It might merely be the equivalent of our annual English remark in March, "This horrid East wind which carries off so many of our old people every year."

Another name, 'Paludism,' is equally badly founded, for there are marshes without malaria and in a great many places malaria without marshes.

We shall not have occasion in the course of this study to say much regarding the clinical side of malaria, so we may incidentally mention here one or two other observations of that master-clinician Trousseau. Whether it was that quotidian (² subtertian) was more distressing and therefore received more persistent and energetic treatment, we know not, but Trousseau remarked that the farther removed the symptoms were from quotidian the more difficult was the cure, thus tertian was more refractory and quartan worst of all in responding to treatment, elsewhere he remarks that quotidian often cured itself spontaneously because, he states, it is "seldom of marsh origin." This seems an inadequate reason, at least a *non sequitur*. So much more resistant was quartan that there was an imprecation or malediction in common use. *Quartana te teneat*—May a quartan seize you! Trousseau noted that in places where marsh fevers are endemic, or, as we would say, in malarious countries, fevers such as typhoid, or pneumonia, or pleurisy might begin as an intermittent fever, even in the absence of any concomitant malaria, and he advises waiting for a few days before starting quinine treatment, since, if the condition is not malarial but typhoid, for example, the quinine will fail. This is well known now to all who work in the tropics. The converse of this was also known to him, what he called *malaria larvée* or masked malaria, in which malaria

symptoms might simulate epilepsy, apoplexy, pneumonia, cholera, severe trigeminal neuralgia, and other conditions

But if to those in England or on the Continent, especially in France, who saw the more typical cases the difficulties in diagnosis were comparatively easily overcome in the days before the use of the microscope to that end, it was not so with those practising in the tropics where association with other diseases was more likely to occur and confusion to arise. Severe cases of the bilious remittent type might be mistaken for yellow fever, in fact Chisholm, while clearly recognizing the difference, designates it "yellow remittent fever." He gives an excellent detailed description of it and one can well understand it being mistaken for yellow fever itself by those with less experience. He prefaces his description by an account written from New York in September 1817, stating that—

We continue under the rigid system of quarantine to enjoy an entire exemption from yellow fever, except that it exists at our lazarette where ships from the tropics are quarantined. Not so in Charlestown, South Carolina, where the disease prevails with great mortality, cutting off from sixty to seventy persons weekly

In this regard, however, it is well to note that at Charlestown at that time quarantine was a dead letter, intercourse between it and the West Indies, particularly Havana, was unimpeded and the majority of the Charlestown physicians "disbelieve in its contagious nature and identify yellow fever with bilious remittent, the product of their marshes!" The fact, however, should be noted that the disease prevailed at Charlestown in the marine hospital before it appeared in the city and was almost certainly, therefore, yellow fever. He remarks further that there is no need to shut up the members of a patient's family "for the sphere of infection in no case exceeds ten feet and generally is less than six feet, all beyond that remained untainted." One wonders on what evidence he bases such a statement.

Chisholm then goes on to describe in no little detail what he calls yellow remittent fever and we think it will not be unprofitable to dwell a little on this because from his account of the symptoms and of the findings post mortem it would seem that he does not himself always distinguish the 'yellow remittent' form of malaria from true yellow fever, in spite of his statement that they ought never to be confused by anyone with experience.

The causes, he affirms, are exhalations from marshes, stagnant water and thick woods or damp, unventilated places, and decomposition of wine leaking from casks on board ship. "Ships con-

taining wine in their holds, in a state of decomposition, are generally extremely sickly " The attack may be ushered in by dysentery lasting for two to five days, but may assume from the onset the type of quotidian or double tertian fever Those living on the lower floors of barracks had a large proportion attacked, thus, at Fort William Henry, at the mouth of the Demerara River, the soldiers on the lower floors all suffered with remittent fever and exhibited the more severe types of symptoms, whereas the officers and their attendants who occupied the upper floors suffered from slight attacks only of remittent fever, or had the intermittent type The temperature might range between 102° F to as high as 112° F (he states) with a bounding pulse up to 140 a minute Actual hæmorrhage was uncommon but many showed an extensive petechial rash and all were jaundiced, and in later stages became comatose, with sighing and fainting, subsultus tendinum and hiccough But, whereas in yellow fever, the voice is weak and thin he states that in yellow remittent fever, in spite of the intense prostration, the patient's voice is "as strong, full and sonorous as in health"—curious phenomenon Nausea is present from the outset and actual vomiting occurs on the third day, "accompanied with what has been improperly considered as diagnostic of yellow remittent fever, a discharge of black- or brownish-coloured fluid of the consistence of coffee-grounds" These are Chisholm's own words and can best be accounted for by saying that he was confusing the disease he sets out to describe with cases of yellow fever He notes also that in late stages there is suppression of urine There was considerable variety in clinical type, thus Chisholm records the case of a gunner whose first paroxysm with violent chills and delirium occurred at midnight and who died in coma two hours after, in others death did not take place for twenty days Some of these more prolonged cases might have been enteric fever, he mentions that in an autopsy of one of these he found the mesenteric glands enlarged and several filled with pus

That the majority were of a malarial nature is probable, for he speaks of the disease as "the endemic of the marshy and woody tracts of Asia and more especially of India [this would seem to rule out yellow fever] and many similar tracts of Africa and North and South America" [where yellow fever was common] Further, he states that it was similar to what was known as Walcheren fever [In reference to this a medical officer wrote that in six weeks he had sent nearly 8000 sick to England and would be sending 3000 more, the prevailing disease being intermittent fever, but some showing remittent fever of the worst

form "often seen in the West Indies"] The disease prevailed from the Carolinas of North America to Surinam in the South and the Gulf of Mexico, being found on the shores of South Carolina and Georgia, the Floridas, the banks of the Mississippi, the shores of New Spain, Yucatán, the islands of San Domingo, Cuba, Jamaica and some of the Windward group corresponding in climate with the sunderbunds of Bengal and other parts of the East where there were forests, undergrowth and jungle, and where in rainy weather there was abundant vegetation in a state of decomposition.

The condition was, it is clear, not well defined. At St Christopher's in 1812 deaths from it were many, "more frequent than recoveries." Chisholm found at autopsy inflammation and adhesions of the cerebral membranes and "large quantities of black matter in the stomach, gall-bladder and small intestine." In one regiment 118 died out of 422 attacked. "Bark was tried, but with the very worst consequences." He concludes that it may have been "typhoid yellow remittent fever" (perhaps the same as *malignant pestilential fever* which is referred to later) which he had seen in both East and West Indies.

There are further reasons for believing that some of the cases occurring in the West were yellow fever. Thus, a vessel, the *Regalia*, arrived at Barbados in 1814 from Sierra Leone where slaves had been sent on board from the hospital. In spite of "fumigations, ventilations and whitewashings" of the ship every white man on board was attacked, though there had been no sickness among the crew prior to embarkation of the slaves.

Again, in 1819 among a regiment stationed in Trinidad a marshy fever acquired increased contagion through influx of Spaniards in a deplorable state from the Spanish Main. Stimulating treatment, 'three bottles of brandy a day for several days,' proved very successful. According to Chisholm these outbreaks at St Christopher's, Barbados and Trinidad show that "typhous infection does exist, perhaps does originate, within the tropics."

The clinical symptoms, as already stated, of some of the cases were strongly indicative of yellow fever existing among them, and this is further borne out by the post-mortem findings, the chief of which were

liver in a loose, dissolved, putrid state or with consistence and feel and colour of *rotten cork*. Little bile in the gall-bladder and that little is black, ropy and granulated. The duodenum may be inflamed, with marks of gangrene. In the stomach blood vessels distended and containing black mucus and fluid resembling coffee-grounds. The whole body of a deep yellow colour.

To save returning again to this subject a few words may be added here regarding the treatment of this condition, as recommended by Chisholm. To us it seems to have been very drastic, but he claimed that it was wonderfully successful. First, copious bleeding, "fully three pounds of blood being taken away." He reports a case of cure [should we say 'recovery' ?] in twenty-four hours with ability of the patient to resume his duties with his accustomed alacrity. Should the disease persist, the bleeding should be repeated and accompanied by purging. If the patient still does not respond satisfactorily, recourse is had to mercury, 5 grains of calomel every two, three, or four hours till convalescence, usually in three to four days. In some cases he gave 20-30 grains every three or four hours.

I can confidently assure the young practitioner [he writes] that not a single patient in my practice died, even under the worst form of the disease, if mercury could be introduced in sufficient quantity to produce ptyalism. Tonic medicines are worse than useless. Bark is decidedly mischievous and never beneficial [although he believes the disease to be malarial].

To sum up, he advises "Bleeding to the extent necessary, plentiful alvine evacuations, mercurial ptyalism and cold affusion." How the patient must have prayed for death!

He notes the evil consequences of fear, that if a man comes to the tropics with the notion that if he is attacked by any of these fevers he will die, "it generally becomes so", otherwise he is convinced that the tropics, under common circumstances of life and under the exercise of temperance and prudence in the conduct of it, are not more injurious to the human constitution than a temperate one.

About the same time as Chisholm was recording his experience in the West, Dr James Johnson, a naval surgeon, wrote on what was probably the same disease in the East under the heading of *Batavian* or *Edam endemic fever*, which, he said, might be so severe as to resemble yellow fever. It is well to consider this question, for yellow fever has not been known in the East.

At the time of the naval blockade, early in the nineteenth century (Johnson's book on the *Influence of Tropical Climates on European Constitutions* was published in London in 1813), the hospital was situated at Onrust. There was always a mist in the morning arising from the low-lying swampy grounds about Batavia. Onrust, a small island, was well cleared of trees, undergrowth and jungle, was flat, and, except one spot daily covered

twice by the tide, free from marsh. The hospital buildings were good, with abundant space and excellent ventilation, situated three miles from the mainland. Against all medical opinion and advice the Commanding Officer ordered the sick to be removed farther from the mainland to the island of Edam, nine miles out, which was covered with long grass and jungle and in parts stagnant marsh "where pestilential miasmata in a concentrated form issued from every foot of ground." What happened to the transferred patients is not mentioned, but at different times sixty soldiers in good health landed at Edam for duty. In six weeks thirty-one of them died and of the twenty-nine who re-embarked when the blockade ceased, twenty-two died at sea and seven were sent to Malacca hospital where "all or nearly all" of them shared the same fate.

As the soldiers fell ill on Edam, a party of sixteen marines was landed for night duty. After a short interval (stated, in the only instance where the time is given, as thirteen days) all were seized with fever, thirteen died, one was sent to Malacca hospital, and two recovered. The number of seamen who succumbed is not known. As regards the symptoms, many were jaundiced, and vomited "black bilious stuff," some became comatose at the very start—cerebral malaria. Fatal days were the third, fifth, seventh and ninth days from the onset, some died on the eleventh or thirteenth. Very few of those who spent a whole night on Edam recovered, Johnson knew of four only. In several the fever developed into an obstinate intermittent after they left Edam and were at sea.

The Dutch in Batavia usually resided on elevated ground a few miles from the coast, away from the swamps, and they enjoyed fair health, but the Dutch ships, according to information obtained from the residents, generally lost half to three-fourths of their crews between the time of their arrival at Batavia and the departure of the vessels for Europe.

The collection of information as to the prevalence of malaria in early times hardly comes within the scope of this work, except in so far as it may touch upon the question as to the connection which grew up in people's minds between swamps, marsh air and malaria. Before dealing more specifically with the question of malaria and swamps, a few words on the prevalence in those times may be of interest. We may speak first of Europe.

In his investigations into the history of malaria in the Netherlands Swellengrebel brings forward evidence to show that the

so-called 'swamp fevers' and epidemic outbreaks of disease attributed to this cause were not all malaria, and also that as regards outbreaks of malaria, ætiological factors other than, and in some cases more important than, marshy soil were concerned. Such, for example, as introduction of infected labourers to carry out reclamation of land, of soldiers from malarious countries in time of war or on special expeditions—the Walcheren expedition in 1809, for example, when nearly 30,000 of the personnel were attacked by fever and 3469 died, and Groningen in 1826—or where medical aid and hospital accommodation were insufficient, or water-supply and nutrition were inadequate, and scavenging not properly carried out. The term 'swamp fevers' was really of a group character including several diseases, among which were included malaria, enteric fever, dysentery, typhus, relapsing fever and pulmonary affections, and perhaps influenza.

In the Rhine Province serious outbreaks were recorded in 1825, 1834 and 1843, and for these the existence of marsh-land and stagnant collections of water were held responsible. Drainage was undertaken, tracts of marsh transformed into arable land and malaria steadily declined and at the same time agriculture improved and poverty was reduced. In 1844 Professor Marx of Göttingen University wrote

If one labours continuously at the carrying off of stagnant water and prevents further collections, if in districts where rice and hemp cultivation are spoiling the air, care is taken to plant trees, if surface drains are kept clear, old town-moats filled in and efforts made at the same time to provide clean drinking water, good food and dwellings, the cold fevers [malaria] cease even where they appear to have acquired indigenous rights

In our own country agues were common less than a century ago, notably in the Fens of Cambridgeshire and Lincolnshire, in the marshes of the Thames Estuary, in Kent, Essex, and south coasts, on the Romney and Pevensey marshes, at Bridgwater near the Bristol Channel. Though it varied in prevalence from year to year malaria was never absent. It prevailed in London, as recorded by Defoe, but it must be remembered that the London of his day was surrounded by marshes. The disease is believed to have killed James I and Cromwell and to have attacked Charles II. It was present in London itself as recently as 1859, in 1850 and 1860 between twelve and sixty per thousand admissions to St Thomas's Hospital were on account of ague. The building of the Thames Embankment was medically, as well as from the engineering point of view, a good move, for it necessitated

drainage, and reclamation of the land at the margin of the river reduced the incidence of malaria. By 1864 the disease was rapidly disappearing in England as the result of agriculture, drainage, better housing and living, after existing there for at least twelve centuries. The Venerable Bede in his *Historia ecclesiastica gentis Anglorum* records a case in the Fen district in the seventh century.

We cannot, however, dwell on this, our concern is with warm climates. Malaria proved a formidable obstacle to the work of pioneers, discoverers, travellers and settlers in Africa. A little more than a century and a half ago an Englishman by the name of Bolts, who was in the service of Maria Theresa, went, in 1776, to Lourenço Marquez to found an Austrian company to trade with the East Indies. He came to terms and made treaties with the chiefs of Delagoa Bay, but negotiations were brought to an end by an outbreak of fever which seems to have been malaria and which carried off nearly all the Europeans.

In 1841 the British Government, at the instigation of Sir Thomas Fowell Buxton, the philanthropist and anti-slavery enthusiast, sent out a Niger Survey expedition under four naval officers. At that time philanthropy reigned supreme over common sense. Dickens satirizes the state of things in *Bleak House*, in his account of Mrs Jellyby's mission to the natives of Borriaboola Gha. The Government expedition, ignoring altogether the unhealthiness of the Lower Niger, had for its aim the establishing of a model farm at the junction of the Benue and the Niger, and at the same time the spread of Christianity, suppression of the slave-trade and incidentally the zealous pushing of the sale of Manchester goods. As might be expected of an expedition with such varied and, in a way, such conflicting aims, little attention was paid to the things conducive to the maintenance of health—the members may have been ignorant of them—fever caused great loss of life and wrecked the undertaking.

Livingstone, in the account of his travels, repeatedly mentions malaria. One or two references may be given. At Lanyanti in June, he says, cold east winds prevail and as they come over the extensive flats inundated by the Chobe and other districts where pools of rain-water are drying up they may be supposed to be loaded with malaria and many cases of fever follow. Again, speaking of Loanda in February, he says that so long as easterly winds prevail all enjoy good health, but from January to April the winds are variable and sickness general.

The unhealthiness of the westerly winds probably results from malaria, appearing to be heavier than common air and sweeping down

into the valley from the western plateau The gravitation of the malaria from the more elevated land of Tala Mungongo towards Cassanga is the only way the unhealthiness of this spot on the prevalence of the westerly winds can be accounted for. The banks of the Quango, though much more marshy and covered with ranker vegetation, are comparatively healthy, but thither the westerly wind does not seem to convey the noxious agent.

This peculiar distribution of malaria must have been very puzzling with the then current ideas of malaria infection.

In another place he says "We were again brought to a stand by fever in two of my companions. We were using the water of a pond and [a Portuguese] having come to invite me to dinner drank a little of it and caught fever in consequence." Although Livingstone relates the incident in these words he would seem to have a doubt, for he continues

If malarious matter existed in water, it would have been a wonder had we escaped, for, travelling in the sun, with the thermometer from 96° to 98° in the shade, the evaporation from our bodies causing much thirst, we generally partook of every water we came to. We had probably thus more disease than others might suffer who had better shelter.

We shall see later that Manson was, for a time, under the same impression that malaria was contracted by drinking water.

Livingstone found that in the interior the fevers were much more virulent and more speedily fatal than on the West Coast. He remarks that from 8° South they almost invariably take the intermittent or least fatal type, and their effect being to enlarge the spleen, a complaint best treated by change of climate, we have the remedy at hand by passing the 20th parallel on our way south.

In those days of uncertainty, temperature, winds, exposure, proximity to water, the drinking of infected water, the changes of the moon all were thought to play a part in causing attacks of malarial fever. To quote Livingstone once more, we find "A sudden change of temperature happening, simultaneously with the appearance of the new moon, the commandant and myself, with nearly every person in the house, were laid up with a severe attack of fever."

Once he seemed to come within hailing distance of connecting malaria with mosquitoes, but it may have been merely a chance observation, at all events it was not followed up.

I was seized by a severe tertian at Mazaro [he writes]. My fever became excessively severe in consequence of travelling in the hot sun.

At Interra we met Senhor Asevedo who : . immediately ten-

dered his large sailing launch which had a house in the stern This was greatly in my favour, for it anchored in the middle of the stream and gave me some rest from the mosquitoes, which in the whole of the delta are something frightful

One last extract from Livingstone

Kilmane is very unhealthy A man of plethoric temperament is sure to get fever I had an opportunity of observing the fever acting as a slow poison They [the patients] felt out of sorts only, but gradually became pale, bloodless and emaciated, then weaker and weaker, till at last they sank more like oxen bitten by tsetse than any disease I ever saw

We cannot leave the subject of Africa and its explorers without mention of Alexandrine Tinné She was an accomplished and daring horsewoman, with a gift for languages, speaking several, among them Arabic Her explorations were mainly along the Nile and about the Sahara and Bahr-el-Ghazal She was accompanied by her mother and her aunt, but both of these died from blackwater fever In 1868 she set out to cross the Sahara from Tripoli to Lake Chad, intending to go thence to the Upper Nile, but on the way she was killed by Berbers She was only thirty-three years of age when she died and for long after her death she was regarded and revered as a demi-goddess

The climate of tropical Africa, in the low-lying littoral districts at least, is damp, equable, enervating and highly malarious In the higher ranges and in East Africa it is less malarious and better suited for European settlement, the country being well-watered, game plentiful, the air bracing and healthy, and the nights cool, even cold It must not be forgotten that neighbouring districts are heavily infested and that importation of infection is easy Moreover, deforestation plays a considerable part in changing a climate, woods form an important factor in maintaining atmospheric equilibrium, where they are, rainfall is more frequent but not very violent, and on the forest being cut down the frequent shower is exchanged for the torrential downpour at longer intervals

In India many large and potentially fertile tracts have remained uncultivated because of malaria This is a convenient opportunity for a few words on the all too prevalent idea that people are prevented from cultivating land or are driven away by malaria Thus, in Yunnan the disease locally known as *Charegch'* is really malaria, mostly subtertian, and from time immemorial has retarded the development of the people and the province which is rich in

minerals The disease is ascribed by the inhabitants to poisonous gas arising from decaying vegetable matter in the valleys The disease is still rife there, for in a recent journey from Kunming (Yunnanfu) to the Burmese border, a distance of 700 miles, a medical party investigated the inhabitants at twenty-seven villages and found among the children a spleen index between 12 and 100 per cent and a parasitic index ranging from 7.6 to 68 per cent

Relative to the question of malaria preventing cultivation, Hackett has stated relative to malaria in Italy and the Roman Campagna, that if malaria prevents a farmer living on his land he cannot develop it properly and his small-holding becomes unprofitable, and further land reverting to its primitive state forms marshes, which afford breeding-sites for mosquitoes and consequent increase of malaria to those living near, and so the cycle is completed to begin anew It is quite true that absentee landlordism and undeveloped properties are characteristic of regions where malaria is rife, but this is not the whole matter, for we all know of places of advanced cultivation but where malaria prevails Malaria, therefore, does not necessarily prevent cultivation, and the reverse also is valid, cultivation does not necessarily eradicate malaria, although there are places where intensive cultivation has been followed by, if it has not been actually the cause of, disappearance of malaria

To return to India Martin notes that malaria is more prevalent in the autumn months and that the drying up of marshes and of river-beds is especially associated with increased prevalence Between August and the ensuing January, when he was in Calcutta, there were 460 deaths among 1200 British inhabitants, at Fultah 240 deaths, mostly of Europeans, in an epidemic in 1756 between August and December, and less than 30 survived Lind, when he was surgeon of the *Drake*, Indiaman, speaks of the fever which raged in Bengal in 1762, as of the putrid and remitting type "ending fatally during the third fit, which is generally the case"

According to Cilento, who has investigated the question of malaria in Australia, that country was probably free of the disease before the advent of the white man, in spite of the fact that a third of it lies within the tropical zone The endemicity is, on the whole, not grave, though it is of importance in Papua and New Guinea Outbreaks in Australia have usually been associated with disturbance of virgin soil by a rush of prospective miners or gold-seekers The history of malaria in Australia, though brief, is not without interest

In 1864 the population of Burketown, Queensland, was small,

76 Then Malays from Java introduced the infection and 50 of the 76 died and the settlement removed to Sweer's Island at the mouth of the river. The first medical description of the disease in Australia is that of Dr J A White who in 1867 met with it in the Gulf of Carpentaria. What was known as 'Gulf Fever' almost certainly comprised other conditions also, such as simple continued fever (whatever that may be), heatstroke, among them. Twenty-two years later Dr P M Wood noted its prevalence in the Northern Territory, and in 1890 it was observed in Townsville, Queensland, and near the Darling River, New South Wales, the latter district, it would appear probable, being infected by return of patients from Queensland. In 1910 there was an outbreak on the goldfields at Kidston, where among a population of 400 or thereabouts there were 110 cases and 24 deaths. Infection in this instance is believed to have been introduced by miners from New Guinea.

The disease may be said to be limited to the north-west coast of Western Australia, to the Northern Territory, the coastline of the Gulf of Carpentaria, Cape York Peninsula and the Northern Pacific slope down to Townsville, but there is no slight menace from the Dutch East Indies which are distant only a three days' journey.

Passing to the Western hemisphere we find no proof of the presence of malaria in America prior to the Spanish Conquest, for the Gulf of Mexico in the time of Cortez and Grijalva was well settled and prosperous and neither of them mentions any sickness among their troops in any way resembling malaria, although prior to embarking on the campaign of conquest they had stayed for six months, March to August, in and about Vera Cruz. In more recent times the coast has been highly malarious.

Neither was Peru malarious in those days, in fact Guayaquil in the sixteenth century was a health resort, Herrera and Monardes both wrote of its salubrity, whereas now it is malarious in spite of modernization and sanitation.

Yet another part of the country, the Amazon Valley, seems similarly to have been free of it in early days of recorded history. In 1542 Francisco de Orellana left Pizarro near the source and journeyed with a party of over fifty to the mouth of the river. Three met death at the hands of Indians, seven died of starvation, the other forty got through in safety and no mention is made of any fever or sickness of any kind. Again, twenty years later General Granua came down with a rebel army and all were in good health. In expeditions in 1609 and 1637 no mention is to be found of any fever. It is the general belief that malaria was

originally introduced either from Europe or by the slaves from Africa

It is only right to state that a condition under the name 'modorra' mentioned as proving very fatal to members of Pedrarius's expedition to Darien early in the sixteenth century (1514) may have been malaria of a malignant type with cerebral complications, the symptoms being lethargy, heavy somnolence and coma, but nothing is said of convulsions or other forms of malaria and it is not likely that all would be of the cerebral type. With this possible exception we may say that malaria came in after the Spanish Conquest, and not immediately after for there is no evidence of its being common for fifty years or more after settlement. Thus, in the seventeenth century five cases only are recorded as occurring in Virginia, but by the next century it had spread all over the State

We will not dwell now on the fact that in many places malaria, previously a scourge, was passing before we had any knowledge of the connection between mosquitoes and infection. A reference or two only may be made, since the question is one not strictly tropical. Thus, Sydenham (1624-89) described in no little detail the intermittent fevers prevalent in a large part of England and Scotland, and the 'marsh fevers' continued in certain districts of England till the last quarter of the nineteenth century. Even later it was demonstrated that sufficient *Anopheles* remained to reproduce indigenous infection when reintroduced by soldiers returning from abroad in the European War of 1914-18.

Again, at the beginning of the nineteenth century Holland was almost as malarious as the Agro Romano, but for some years past it has been not only strictly focal in distribution but mild in type and degree. A hundred years ago Rochefort and the mouth of the Gironde were intensely malarious, now the disease is practically unknown there. The same will apply to Wurttemberg and the Harz Mountains in Germany.

In the West, a century and less ago, malaria was rife in the low-lying valleys of Minnesota and in Michigan and round the Great Lakes, now it is practically absent. In the first half of the nineteenth century New York and Philadelphia and their environs were intensely malarious, at the time of the Civil War it was probably the chief cause of death in the southern states, blackwater fever and coma being common. In the last decade of the century many cases were reported in New Orleans, now there are none.

The only causes assignable for these remarkable changes are the general advance in civilization, the clearing and development of land for agricultural purposes and the establishment of industries. Since the end of the century, of course, we have had the results of diffusion of knowledge of the part played by mosquitoes and the mode of securing protection against them, aided by the intelligent use of quinine, not merely as a remedy for symptoms, but as a protective or preventive in some degree.

2 MARSHES AND MALARIA

The intimate association of the proximity of swamps and marshes with the prevalence of malaria, agues, 'marsh fevers' has been common knowledge for hundreds of years, the point that puzzled investigators was that there were marshy plains where malaria did not prevail and, again, when a marsh became flooded more extensively and deeply malaria was less prevalent. Thus Trousseau states in his Lectures. Marsh miasma is a poison only to the human species [a purely dogmatic statement, for in his day the parasite had not been discovered and of course he was quite unaware that birds, monkeys and other animals suffer from malaria]. It is common, he says, in hot, low, damp climates, but is not due to humidity alone because the miasm only acts when a considerable surface is covered with water [he apparently did not know that a very sure hunting ground for mosquito larvæ on the Continent is the holy-water stoups in the churches], or the soil is impregnated and evaporation takes place producing telluric emanations which constitute what we call 'marsh miasmata' and that no great inconvenience is caused so long as the ground is submerged.

Du Chaillu noted the same in Africa. The coast fever is caused, he says, by miasms from the immense swamps, during the rains streams overflow and vegetation grows luxuriantly, and when they retire a heavy deposit of fertile mud remains to enrich the soil and also to breed fevers and other diseases. When the dry seasons come the miasms rise and are dispersed.

I have no doubt [he writes] that the great mortality of several African exploring expeditions arose, in a measure, from the mistaken supposition that the dry season was the safest for such ventures. It is only after a severe and continued drenching, when the rainy season is fully set in, that African rivers should be explored.

We have already noticed Livingstone's views in this respect of ponds, marshes and malaria prevalence, though he seems to have inclined to the idea that infection was acquired *per os*.

The association of swamps and malaria in days before the mosquito theory was advanced is well exemplified by the history of the disease in Mauritius. In fact, it was with such epidemiological records that true research began.

Between 1812 and 1836, and between 1859 and 1866 there were only 262 admissions for malaria in Mauritius, or 0.4 per cent, and these occurred, not among the indigenous population, but among troops brought there shortly before from China and India. The country was remarkably free until the disastrous outbreak of 1866, and since then it has wrought much mischief. We may say now that *Anopheles gambiae (costalis)* was imported there from East Africa in 1865, and in the following year coolies, many of them doubtless with latent malaria, were brought from India to work on estates. Thus there were present, the source, the vector and a non-immune population. Between 1867 and 1869 among 3201 troops there were 5048 admissions, or 50 per cent more than individuals, and in this small colony it is said that 31,920 persons died of the disease.

Up to this time the coast and the level country which afforded a rich soil for growing coffee, indigo and cotton had been allowed gradually to go out of cultivation and the higher levels were encroached upon and sugar plantations were laid out. This necessitated deforestation with consequent change in the hydrology of the country and the former torrents of the hillsides became mere trickling streams, they did not reach the coast but sank into the ground producing small swamps. In 1865 rains were heavier than usual and the swamps became larger and in the hot weather of the following year an outbreak of malaria started and soon spread over the whole island, where it has ever since remained endemic.

The sequence was similar to that which is seen to occur in other tropical regions at the present day. Low-lying, badly drained areas near the coast became converted into swamps by the heavy rains. This condition would vary in extent and duration with the nature of the soil, the amount of slope, the drainage and the rainfall, but would usually persist for several weeks and the swamps become the home of innumerable insects. Among the first to breed would be the mosquitoes, the females will oviposit repeatedly throughout the season and the swamps swarm with larvæ and pupæ. This breeding-ground, fortunately, is also a death-trap and an enormous number, probably the majority, fall victims to predaceous enemies, such as the dragonfly, the young nymphs of which feed on the larvæ. History has shown us that

in malarious districts of warm countries the fever usually appears (or, if endemic all the year round, begins to increase) at the start of the rains, gains in extent and severity with increasing rainfall, remits usually at the height of the rains, if these are very heavy, to reappear again at the cessation of the rainy season. We know now the explanation of this sequence—the rains producing pools and breeding-sites for mosquitoes, the heavy rains washing out the pools and carrying away the larvæ and pupæ, and the subsidence again resulting in pool-formation or residual collections of water. Thus, we can understand that, except in the neighbourhood of marshes, rivers, ponds, the disease is more common in wet years than in dry. In India, in 1868 and 1871 the north-east monsoon almost failed, rivers were drying up and leaving residual pools in which breeding of mosquitoes took place and there was an increase of malaria in Madras. The general principle may be summed up by saying that as regards configuration and altitude the disease prevails on low-lying land, becomes less as we ascend, if the surface is undulating the deepest localities are attacked first and most severely. If we find endemic foci high up, these are declivities, valleys or pocket-like depressions in an elevated plateau. Hence an outbreak will decline as a damp or marshy soil dries up, as it will also when the ground is completely covered, to reappear as the surface clears and puddles and ponds form. We see this exemplified in the inundations of the Nile, the Indus, Ganges, Euphrates, Niger, Mississippi and elsewhere, or, on a smaller scale, in rice-fields.

The association of groundwater with malaria prevalence was stressed in 1898 by Sir Leonard Rogers (then Captain Rogers, I.M.S.) in a paper read before the Epidemiological Society. In Lower Bengal fever was at its lowest when the land was entirely submerged and at its maximum during the time of rapid drying of the soil. Manson did not agree that there was any real association between the two, but believed that there were intermediate causes then unknown, and McLeod considered that stagnation was of far greater import than mere level of groundwater and that in the irrigated districts of North-west India it was to this stagnation that the alarming increase of fever was due and the same idea gained confirmation from Pringle's reference to the disastrous effects of irrigation unscientifically carried out in the country between the Upper Ganges and the Jumna.

We have seen above how malaria increased when woods were cut down and cultivation neglected in Mauritius, and how the breaking up of virgin soil leaves holes for collection of water and

facilitates mosquito breeding—not, as used to be thought, the setting free of miasm and vegetative ferments. Another good example is seen in the Southern States of America which before the Civil War were well cultivated and drained and the more severe forms of malaria were hardly known, except in some low-lying and badly-drained swampy areas. Between 1866 and 1874 much of the land was lying waste, drainage became defective and malaria rife, or, as it was said in those days, “the malarial poison acted with increased virulence.”

After this digression we return to Mauritius. The following are the words of an eye-witness of the epidemic there in 1866, and a more graphic, heartrending account it would be difficult to find. It was written by Colonel Nicholas Pike, American Consul at Port Louis.

Those who inhabited Port Louis during the terrible mortality in 1867 and 1868 will never forget the sad spectacle the city presented daily. Fever! fever! was the only word on every lip, the only thought in every heart. Mourning and desolation everywhere. Scarcely a person visible that did not wear the garb of woe. Song and laughter had ceased.

Funeral trains were met at every corner. Relays of men were kept night and day digging the graves. The owners of undertakers' shops that sold mourning, and the apothecaries, must have made fortunes. The numerous druggists' shops were so crowded day and night, and so short of hands, that it was with difficulty medicine could be provided. Offices were opened in all directions for the distribution of food, medicine, or advice to the destitute, but all the efforts made by the municipality and private charities could not keep pace with the progress of the wretchedness and distress.

There was no mistaking the appearance of one who had suffered, the pallid, drawn features, the skeleton, bloodless fingers, as if the life-stream had been dried out of them, and the slow dragging step marked but too plainly the victims.

It was distressing to pass through the streets in every corner was some poor creature, suddenly struck down, and crouching on the ground to die. In the outskirts of the city and country roads the victims were so numerous that the police and sanitary committees were insufficient to succour half the poor wretches, and many died by the roadsides before help could be brought to them.

Near Roche Bois I have seen them lying in groups, dying and dead. Not a house within a radius of half a mile from the one I then occupied had a living person in it, except a shop belonging to three Chinamen, two of whom died later.

In many cases, as soon as a Malabar got the fever, he would hasten to his house and shut himself in to die, for such was the fear of it, to be attacked was the tocsin of death to him.

I visited many families, and the scenes I witnessed will never be effaced from my memory. A poor Indian, whom I had cured for

the time being, came and entreated for help to a comrade. It was night and I was tired and had gone to bed but I dressed and went with him. After a long walk we came to a hut, and as I approached I heard groans and lamentations. When I entered the scene baffled all description. A small coco-nut oil lamp dimly lighted the interior, adding horror to the scene. It was inhabited by a man and his wife, and a number of children. The mother lay dead in the middle of the hut, the man hanging over her in an agony of grief. Her baby, still living, was clasped to her heart, and seeking to draw its life-sustenance from her cold breast. The other children were all stricken with the fever, and in its last stages, past human help. Of course, all I could I did, but help had come too late to do little more than assist at the burial.

One dreaded to ask the news, as one was quite sure to hear of some friend ill, dying, or dead, and often buried before you knew of it. Parents had to rise from their sick beds to nurse their children, and these again had to drag their weary limbs to follow a beloved parent to the tomb, though frequently too weak even to do that.

No change of weather seemed to arrest the plague. Intense heat or cold, heavy rains or dry, mild, calm days or sharp breezes, all were alike fatal. The brightest morn brought no more hope than the wildest night.

For months the death-rate in the city alone averaged nearly 200 *per diem*. In every street could be seen the mourning weeds outside the doors where death had struck his victim, and this was often the first intelligence you had of the loss of dear friends. May I never witness again the sad sight of those incessant funerals, slowly wending along from morn till night. Here a group of Malabari bearing along some poor fellow, preceded by a priest muttering a prayer, and followed by a few women bearing a copper dish of rice and fruit, and a jug of water to place on his grave.

There comes a slow and stately train with black-plumed hearse and a long line of carriages behind it—one of the rich and respected of the land, anon, a little simple bier, bearing a baby's coffin covered with a simple white muslin pall and wreath, with perhaps only the father and nurse as mourners, then a white-covered hearse, its white plumes and horses' sweeping trappings showing that some fair girl had been cut off in early womanhood.

Occasionally would pass a Chinese funeral, the bier supported by stout Malagash bearers, in their long black gowns and flowing weepers looking as stolid as if of stone, a few carriages following with Chinamen in them, and a person always preceding it, scattering pieces of paper about three inches square, often gilt or silvered, all along the road to scare away evil spirits and prevent their following the corpse to its last resting place.

The connection between swamps, decaying vegetation, miasma and marsh fevers seemed so obvious that the difficulty was to explain why marshy soils were not always malarious. It was noticed, for example, that on the banks of the Rio de la Plata marsh fevers did not occur. This fact was known to all physicians

acquainted with the district and they had no explanation to offer. Again, on many islands of the Parana are marshes innumerable, filling and falling with the rise and fall of the river and containing enormous quantities of vegetable debris. The bottom is always muddy and with the fall of the river "an immense extent of marshy ground becomes exposed. For all that I have not," says Bouffin, "observed a single case of intermittent fever." Humboldt was another to point out the same fact as regards the upper part of the Amazon, in marked contrast with the prevalence of paludal fevers on the banks of the Orinoco and Magdalena. Tasmania and New Zealand were also free in those days. Bongarel, writing of New Caledonia, says, "I do not know that there has been a single case of intermittent fever in spite of the vast marshes that are met with at the mouths of the numerous streams which water the island," and Macculloch, speaking of Singapore in 1839 and its exemption from malaria, says

There is a mystery for which I can conjecture no solution, while every imaginable circumstance is present to render the land in question one of the most pestiferous spots under the sun, it is a collection of jungles and woods, marshes and rivers and sea-swamps, and it is a flat land under a tropical sun, and it is the land of monsoons, and yet it is a land where fevers are unknown.

This assertion was confirmed by McLeod and also by official reports. Alas, it does not hold now, for one of the great difficulties, and one which has been to a great extent overcome in constructing the naval base at Singapore, was the prevalence of malaria.

Elevation of ground, obstacles such as belts of trees, even walls were believed to be insuperable to the spread of malaria and miasmatic fevers. Moulton and Lowndesborough, both in Alabama, are quoted as examples. The former was situated some half a mile distant from a lake, and there was a large farm in the place and all working there enjoyed good health until, in 1826, a dense wood between the farm and the lake was cut down and the farm became "exposed to winds blowing over the marshy lake." Next year the township was severely attacked by malaria, only three or four of the 150 inhabitants escaping the infection. The latter (Lowndesborough) was a plantation a quarter of a mile from a creek with marshy borders, but separated from it by a thick belt of wood. In the winter of 1842-3 this belt was cut down and in the succeeding summer the negroes working on the plantation suffered so severely from malaria that the proprietor had to change their quarters to the other side of the creek where the wood had been left standing. Nowadays, before cutting down a wood which is thought

to be harbouring mosquitoes and thereby making a place malarious, investigation is always carried out to discover the species of *Anopheles* responsible for transmitting infection, otherwise cutting down the trees may get rid of harmless mosquitoes and permit the ingress of noxious species

Malaria introduced into a district previously free from it may produce first an epidemic and then convert it into an endemic focus henceforth Amboina in the Indian Archipelago was free till 1835, a severe outbreak then occurred and ever since the disease has been endemic there and now the place has the reputation of being very unhealthy The original outbreak in 1835 was ascribed to an earthquake, but what part this played *per se* or as sharing in a general disturbance it is impossible now to say

Connecticut is a good example of rise and fall in prevalence When the English first settled there malaria was fairly common, increasing cultivation and drainage brought about its virtual disappearance except in a few river valleys In the 'sixties further developments included large engineering projects, the making of railway cuttings, excavation of canals and suchlike, that is, the formation of borrow-pits and collections of water and multiplication of breeding-sites for mosquitoes, malaria reappeared and soon became widely diffused

We have seen how malaria was for centuries connected in people's minds with proximity to marshes, how they noticed and were puzzled by the fact that living near marshes did not always entail contraction of marsh fevers, that fever might not even prevail there, but there were other points which mystified them, such, for example, as how to account for the presence of marshes with intense malaria at one time and the continued presence of the marshes but little malaria at another This is well exemplified in Angelo Celli's *Storia della Malaria nell'Agro Romano* Celli has endeavoured to trace the history of malaria in Rome and the Campagna from ancient times, obtaining his information, not from medical writers only, but from historians, poets, archæologists, church records, municipal regulations, bills of mortality, in short every available source, and fortunately for the historian ague is a disease which does not need a medically trained man to determine Though the disease became prevalent in Rome after the Second Punic War, about 200 B C, Celli does not believe that it was imported from Carthage It declined again during the days of the Empire until the end of the fourth century A D and early in the fifth when Rome was sacked by the Goths During the suc-

ceeding centuries it was severe enough to hinder colonization until it again declined at the time of the Renaissance. The sacking of Rome in 1527 was followed by another recrudescence and the country remained heavily infected for nearly 400 years.

Reasons brought forward to account for this infestation periodicity are mainly *a priori*. A country while under the ban of severe malaria cannot be properly cultivated nor densely populated and, *vice versa*, districts which become seriously invaded by the infection are abandoned. We see this exemplified in the sites of large Etruscan cities, which are now in ruins and highly malarious. There are evidences of areas where attempts at irrigation have been undertaken and have failed. This is deducible *a posteriori*, for as recently as 1885-90 the State tried to carry out extensive drainage works but failed, attempts at colonization were made but in vain and in 1898 the whole scheme was abandoned.

As Celli emphasizes, the essence of malaria is periodicity, but he assigns to this a far wider meaning than the usual clinical interpretation. The periodicity is daily in the individual, seasonal in type—benign tertian in spring, malignant tertian in summer and autumn—there is periodicity as alternations of mild and severe outbreaks over a length of years (Celli believes in a roughly ten-year alternation) and finally a periodic cycle extending over centuries (see graph) mild in the earliest days and down to about

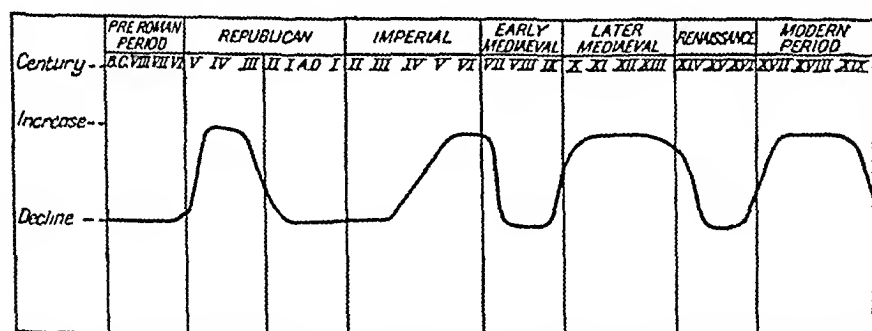


Fig 1—Graph of decline and increase in malaria in the Roman Campagna.
From the *Tropical Diseases Bulletin*

600 B C, severe during the ensuing three centuries, dying down to burst out again in the fifth to seventh centuries A D, then mild again till the tenth, severe till the thirteenth, and then a decline till the seventeenth, and persistent again from the seventeenth to the nineteenth centuries. If there is any real truth in this and the evidence he adduces seems to bear it out, the past half-century is the 'natural' time for a lull—a reduction both in prevalence

and severity—and this increases greatly our difficulty in arriving at any accurate estimate of the value and success of measures taken in hand to reduce it. All we can say is that though these measures are, in part at least, on the same lines as those which before were unsuccessful, they have in the present century been carried out more thoroughly, based on the latest scientific research, infected newcomers have been excluded, quinine has been given, not merely therapeutically but prophylactically (Du Chaillu had done this years before, as we shall see later), the formation of sites and conditions in which *Anopheles* could breed have been avoided, the labourers have been better housed and protected—in short, what is known as bonification in its fullest sense, and the land, which in former days was a hotbed of malaria, has become to all intents and purposes a health resort.

The cyclical prevalence just referred to occurs, it appears, in other countries also, *e.g.* Jamaica, but the history of this island cannot be traced back like that of Italy. Thus, Boyd and Aris in their *Survey of Malaria in Jamaica* find that of late years endemic malaria is almost entirely confined to the fertile coastal plains, where, in fact, agriculture is most successful, the local settled population there is small, most of the labourers come from the interior plateau and are highly susceptible. In the coastal region several foci exist where malaria is unvaryingly severe and intense although in the adjacent country there is comparatively little, except after an exceptionally heavy rainfall when breeding-sites for mosquitoes are formed. In the early years of the present century there was certainly much more malaria than there is to-day, whereas sixty years ago the records point to there being as little then as there is now.

While we are on the subject of reclamation of land from marsh, and making it fertile for agriculture by means of drainage and properly regulated irrigation attention should be called to examples in history of the ill effects of badly schemed or unregulated irrigation. It is difficult to do this without anticipating the mosquito malaria investigations to be dealt with later. We have spoken already of the beneficial effects on malaria in London resulting from reclamation and drainage of the banks of the Thames and the building of the Embankment, but there are other instances from which even better lessons may be learned because they show the ills that may result from a well-intentioned scheme aimed to benefit humanity being wrongly carried out.

We shall have more to say later concerning the building of the Suez Canal and its effects on tropical medicine, here we may

state incidentally that it was malaria that prevented Ismailia from becoming the great port that de Lesseps intended it to be when he planned the construction of the Canal. Again, it was malaria, but this time associated with another mosquito-borne disease, yellow fever, that destroyed the hopes of de Lesseps and the French and cost so many lives and such large sums of money, in their attempts to build the Panama Canal. Two others may be referred to here in illustration of the points mentioned.

An irrigation scheme was adopted in Penryn, at the foot of the Sierra Nevada. The place soon became very malarious and finally an endemic centre. So severe was the infection that the original owners sold or leased their land and left their estates. A plan from which much advantage had been hoped had proved no blessing but a curse and an investigation was asked for. A survey of the breeding sites of *Anopheles* was undertaken and each was mapped out and treated. It was found that the South Pacific Railroad had caused an obstruction to the natural drainage of the district which resulted in the formation of stagnant pools. These were filled in and the cause removed by construction of a permanent drainage of the railroad right of way. That carelessness on the part of the inhabitants themselves played a part was revealed by house-to-house visits when many pails and tubs were found with breeding mosquitoes, pipes were leaking and puddles forming in consequence. Again, the irrigation was not being properly controlled, overflows, leakages were common and seepage from the canals set up stagnant puddles. Supervision and remedying of structural defects were needed. Lastly, labour imported included fresh cases as foci of infection and non-immunes, not protected or looked after, soon became attacked. The explanations for the failure were thus seen to be a sequence of ills. Loss by bills for sickness, insufficient labour in consequence of infection, lack of labourers because the place was acquiring a bad name and volunteers could not be obtained, and, as a result of all these, depreciation of the estates.

We must bear in mind that even under the most favourable conditions relapses may occur, the infection is not at once eradicated, but lies latent, and malaria cannot be got rid of in one or even two seasons.

Coming nearer to our own day, let us glance for a moment at the Sarda Canal Construction (1920-9) for irrigation of the districts Careilly, Shahjehanpur, Pilibhit and Oudh, the largest canal system in the world, 4000 miles in length and watering an area of 7,000,000 acres or more than one-fifth of England. A rise in

malaria which had followed the opening of the Ganges Canal in 1854 was borne in mind and measures taken to guard against it by providing drainage cuts and prohibiting irrigation in places where the subsoil water was already high. A few words will indicate where things went wrong. In the Terai section, where malaria was very rife—the spleen rate was 75 per cent—labour was imported by contractors and the coolies were under no official control. Owing to the intensity of the malaria, the district had a bad name and labour was difficult to get. If the men were pressed too strongly to take quinine, or if they were pricked for a specimen of blood, the coolies promptly absconded. Each year, at the start of the rains in May, construction work had to be suspended till November, and during these months the floods were such that the drains were washed away, the wreckage was buried in undergrowth and weeds, which flourished luxuriantly as a result of the rains. The coolies were housed in grass huts and slept on the floor, their diet was insufficient in quantity and inadequate in quality, the huts were not screened and few, if any, used mosquito-nets.

Owing to the difficulties encountered and the prevalence of the malaria nearly all the known antimalaria measures were tried at one time or another. Elephant-grass jungle had to be cleared to destroy adult mosquitoes in it, even after the use of Paris green, and also because the swamps under it provided sites for prolific breeding. This actual clearing rendered conditions suitable for those mosquitoes which breed in the open and in consequence *Anopheles* appeared in some places where none had previously been seen. Between 1921 and 1926 much drainage and oiling were carried out. After 1926 efforts were concentrated more on the use of Paris green, on fumigation and on treatment of coolies. In the early years of the canal construction, that is prior to instituting antimalarial measures, 96 per cent of the labourers were down with malaria, the contractors refused to continue the work and it had to be abandoned.

This is a fair example of work undertaken for a good end being, temporarily at least, ruined owing to circumstances which should have been foreseen and guarded against—a waste of labour, time and money.

Sufficient has been said, from a general view, regarding the connection between intermittent and remittent fevers and swamps, leading to their being grouped as marsh fevers in consequence.

Important in the history of malaria is a consideration of the views held as to the special ways in which marshes were the cause of the fever. Some of the ideas were strange, fantastic, others were based more soundly on observation. It is less than a century ago that Hensinger on the Continent suggested—in 1844—that what was called in his day ‘miasma’ might turn out to be a poison or a parasite. He, however, was by no means the first to make such a suggestion. Varro in 36 B C and Columella in A D 100 noted the association of marshes and fever and even went so far as to postulate certain organisms too small for the eye to see which might convey the disease by entering the mouth or nose. “Crescunt animalia quaedam minuta, quae non possunt oculi consequi, et per aera, intus per os ac nares perveniunt atque efficiunt difficiles morbos.” Columella also noted that marshes bred mosquitoes armed with stings and that they might transmit disease by their bite. The passage is worth quoting, as of historical interest. It occurs in his work *De Re Rustica*, Lib I, Cap V.

Nec paludem quidem vicinam esse oportet aedificiis, nec junctam militarem viam, quod illa caloribus noxium virus eructat, et infestis aculeis armata gignit animalia, quae in nos densissimis examinibus involant, tum etiam natricum serpentiumque pestes, hiberna destitutas ulgine, coeno et fermentata colluvie venenatas, emittit, ex quibus saepe contrahuntur caeci morbi, quorum causas ne medici quidem perspicere queunt.

Nor indeed must there be a marsh near the buildings, nor a public highway adjoining, for the former always throws up noxious and poisonous steams during the heats and breeds animals armed with mischievous stings, which fly upon us in exceeding thick swarms, as also sends forth, from the mud and fermented dirt, envenomed pests of water-snakes and serpents, deprived of the moisture they enjoyed in winter, whereby hidden diseases are often contracted, the causes of which even the physicians themselves cannot thoroughly understand — (Anonymous translation, 1745)

That the air over marshes contained organic matter was well known in a general way, but one observer noted that if marsh air was drawn through water or sulphuric acid and the organic inclusions were thereby arrested, vegetable matter and organisms, debris of plants, infusoria, insects and, it was said, even small crustacea would be found, and the inference was drawn that “the ascensional force given by the evaporation of water seems to be sufficient to lift comparatively large animals into the air.” Travellers or soldiers in a malarious district were consequently advised to cover the ground under their tents with some impervious

material and, if near a place whence miasma might extend or to which it might penetrate, a screen, preferably of fine gauze or muslin was recommended for use at night, having been found by experience to be efficacious, in order that the microbes might be "scattered, delayed, or enfeebled before being breathed in or swallowed"

This protection from miasma and the possibility of its being driven by wind prevailed for a long time. Lind, as we saw, mentioned the covering of gun-ports and erection of screens on the side facing the shore, and Stanley mentions trees, tall shrubbery and high walls, or a close screen interposed between a dwelling and the wind currents as means of mitigating malarial influence, since the inmates are then subject only to local inhalations. Emin Pasha informed Stanley that he always took a curtain with him, as he believed it to be an excellent protection against the nocturnal miasmatic exhalations. Stanley comments on this and adds "Might not a respirator attached to a veil, or face screen of muslin, assist in mitigating malarious effects when the traveller finds himself in open regions?" This, though apparently new to Stanley, was many hundreds of years old. The mosquito-net, *conopeum*, was known to the Romans and was used by the women, the men regarding it as effeminate. In the Middle Ages its use was advocated as a means, almost the only means, of protection against fevers in marshy districts.

According to Humboldt the smallest marshes were the most dangerous in the tropics because the surrounding sandy arid soil raises the temperature of the ambient air. He does not attempt to explain why this should be more dangerous, presumably the raising force of the heated air elevates the particles, animal and vegetable, to a higher level. Darwin quotes what he describes as an 'admirable paper' by a Dr. Fergusson, saying that the poison is generated in the drying process and that the pools and drying soil are "evidently culture-grounds at a suitable temperature and moisture for microbes which are capable of thriving when transported to the dissimilar pabulum of the human blood."

The theory of infection by the agency of drinking water dates back more than 200 years. The latest authority of any note to hold the same theory was Sir Patrick Manson in the earlier stages of his mosquito-malaria hypothesis.

In 1733 Jussieu, when writing on an epidemic of malaria in Paris which took place two years before, ascribed it to the Seine water contaminated by rotting water plants and *confervæ*, and Meynere of Belgium also notes an outbreak due to drinking marsh

water The idea was fairly widely held We have already seen that Livingstone gave that as one reason of its attacking his Portuguese visitors and in 1869 even so cautious an observer as Parkes mentions that fifteen years before he had visited the marshy plains of Troy and there discovered that those of the inhabitants who drank marsh water suffered from malarial fever all the year, while others who drank nothing but pure spring water suffered only in the summer and autumn Again, Boudin mentions a ship at Marseilles which had taken in a supply of water at Bona, Algiers The source was marshy and malaria broke out on board and of a crew of 229, ninety-eight were seriously ill and thirteen died There are, of course, two possibilities here one, that *Anopheles* larvæ and pupæ were shipped with the water and one or more of the crew were harbouring the parasite, the other that the men were bitten by mosquitoes when shipping the water near the marsh

Another theory closely allied was that after heavy rains malaria organisms in large numbers were washed into the shallow wells, without undergoing filtration through the deeper strata Then, later, on subsidence of the floods these malaria microbes become more concentrated when the uncontaminated flood water ceases to dilute them The advice is, therefore, stressed that for both these reasons water suspected of containing these microbes should be boiled or filtered before being used for drinking

Oiling, though with a different end in view from what is held to-day, is another measure less modern than is generally thought In 1892 a man named Russell—not, I think, a medical man—wrote

The neighbourhood might possibly be made habitable by either drainage or the use of mineral or olive oil to coat the surface of the lake or marsh when at the highest level, so as to cause a film of the oil to be deposited on the ground as the waters subside

3 CAUSATION

We shall see shortly that the dawn of bacteriology as a science led to the discovery of germs as of ætiological significance in malaria, but some of the theories prior to that time are of historical importance, more as indicating the trend of thought of the day than as being of actual value in elucidating the subject Going back no farther than the latter part of the eighteenth and the early years of the nineteenth centuries we find embodied in Trotter's book already referred to, *Médica Nautica*, a "New Doctrine of Fever" emanating from an American Professor of Chemistry

Trotter evidently was not a little impressed by it The doctrine was this

The vitiated atmospheric fluid, by interfering with the pulmonic action, brings on the cold stage, and would continue the same until its termination in death, did not the constitution in the meantime acquire such a habit as to gain a temporary insensibility to its action [the impeded rate of respiration is attended with smaller evolution of heat and oxygene in the lungs, and a proportionate degree of chillness and coldness throughout the body If the constitution cannot acquire this habit, the cold fit terminates in death] This habit being induced, the cold stage abates by reason of the state of direct debility into which the body has been brought, anxiety continues and by the quickening of respiration heat and oxygen are let loose in the lungs and, becoming incorporated with the blood, now warm and stimulate every part with more than usual power and occasion the phenomena of the hot stage, which terminates as soon as the accumulated excitability of the system is exhausted The sweating stage follows of course, as in other cases of subsidence of violent action, for after a time, the exhausted excitability of the animal system allows excessive action to go on no longer, the respiration grows more moderate and easy, the heart beats with less frequency and force, the arterial contractions are also more slow and health-like, and, as the arterial contractions relax, the hydrogene and oxygene of the blood now run together in the extreme vessels of the skin and form the moisture which bedews the surface, and this afterwards flying off by evaporation cools by degrees the whole body down to its ordinary temperature and as the arterial extremities of the rest of the body become dilated by the subsidence of excitement, the other secretions, which had been generally suspended during the fit, now return as before The interval between one fit and the succeeding one will be proportionate to the duration of the habit of resistance acquired The species of fever, whether quotidian, tertian, etc., will depend upon the readiness or quickness wherewith the offending cause gains a new ascendancy over the body or breaks the habit And to the mobility of the body, or ease with which the habit is broken, is to be ascribed, as well the frequency of the returns, as the duration and severity of the paroxysms

All this, though somewhat obscure, evidently proved inspiring to Trotter who says "The anomalous cases of fever, which have puzzled physicians to explain, and nosologists to arrange, are thus very naturally accounted for"

James Johnson, a noted writer on tropical diseases, half a century later is less certain, less dogmatic

What kind of inflammation must that be [he writes] which explodes, as it were, the moment the clock strikes a particular hour, and this for days and weeks together? What kind of inflammation is that which, every second day, terminates in profuse *perspiration* from head to foot, and yet is removed after an interval of forty-eight hours with the symptoms as before, and so on? Do we see real and unequivocal

inflammations pursue this course? Never Are the causes of these *intermittent phlegmasiæ* (if such an expression be not a solecism in medical language) of a periodical or intermittent nature? No They do not accommodate themselves to any particular theory

Audouard in 1848 put forward a theory that congestion of the spleen was the cause of the periodicity of the fever This was never taken seriously, though it was not, perhaps, so foolish as the authorities of his day considered it, for modern research has shown us that means to secure contraction of the spleen and to throw some of its blood into the general circulation—Ascoli's method, it is called to-day—may induce an attack or at least cause parasites to appear in the peripheral blood and so permit a diagnosis to be made in obscure cases of fever or splenic enlargement where ordinary routine examinations of blood-smears yield negative results The thrusting out of parasites into the blood-stream might bring on an attack of ague

Audouard was, in fact, reversing the order of things, *viz*, that malaria is the chief cause of splenic enlargement or endemic congestion The view was held that such a condition might and did occur as a primary disease from mere residence in malarious localities, though more often it was a complication or sequela of fevers, intermittent or remittent Robert Jackson, who wrote at the end of the eighteenth century, found that in the malarial fevers of the West Indies the spleen was generally distended, sometimes even so greatly as to rupture spontaneously He was very angry at the use of new terms for conditions already expressible in terms well known The English, he said, were beginning to use Continental terms, such as 'engorgement' of the spleen for 'congestion'

A German phraseology, now too much in use at home, threatens to become a fashion with us, overlaying our terse and manly language, while it is but ill calculated to fill up the voids in our knowledge The Germans have reduced the art of talking about disease to a system

Audouard was followed by Masurel, an army physician, who affirmed that malaria was due to vitiation of the blood by poisonous miasmata There was nothing new so far, but in its application as accounting for the symptoms it adduced a new theory This altered blood, in his view, acting on the ganglionic system caused the febrile paroxysm, at all events the shivering, which is simply ['] an indication of the existence of a true neuropathic condition As he expressed it, "a depressory heteronervation of the circulatory system" The second (hot) and the third (sweating) stages

were results of the reaction of the organism from the profound disturbance occasioned by the conditions prevailing at the development of the paroxysm. After the paroxysm comes to an end, the 'miasmatic principles' are still in the blood and passing in the circulating blood induce a new change in the nervous system. This is not far removed from Sydenham's view of nearly two centuries before, that the 'morbific matter' eliminated by the sweating accumulates during the apyrexial period till a renewed effort of nature again brings about its elimination by another paroxysm.

None of these, of course, explains the *regularity* of the periodicity in the different forms.

Trousseau was of opinion that the cause of the intermission was closely connected with, and acted by way of, the nervous system, but he was quite candid (as we would expect such a wonderful clinician to be) in confessing that he did not know what the cause was. This we *do* know, he says, that the intermission pertains essentially to the organism and not to the action on it of an external cause, although we see it occur in physiological order without appreciable causes, and in the pathological order under the influence of the most diverse causes, *one of which is the poison of marsh miasm*. Trousseau was most emphatic in classing intermittent fever with the neuroses because of the suddenness of invasion and the rapidity of disappearance of symptoms, of the violence and fleeting character of them, of the disorder through the whole system which, in the pernicious forms, may endanger life, he classes as nervous also the 'deceitful feeling of security' in the intervals between attacks. Finally, the symptoms in 'pernicious masked fever' are nervous, that is they occasion disorder in the nervous centres or the ganglionic nerves. He mentions the German idea that pernicious symptoms were ascribable to emboli of pigment and goes to considerable length to refute the contention of German physicians that the pigment is manufactured in the spleen and passes into the portal vein and so to the liver, the inferior *vena cava* and the heart and thence into the general circulation. Intermittent fever, they maintained, caused hyperæmia of the spleen and this organ manufactured much pigment. We need not dwell on Trousseau's refutation of this hypothesis, suffice it to say that the pigment, he remarked, was altered hæmatin, was formed from the blood and could be found in the liver, spleen, lungs, brain, everywhere, even outside the vascular system, that the pigment was permanent and, therefore, the symptoms should also be permanent, and, he ends triumphantly, the fact that the

pigment is permanent while the symptoms are intermittent is sufficient to show the fallacy of such an hypothesis

As already mentioned Hensinger in 1844 suggested a parasite as the cause of malaria, but Mitchell of Philadelphia in 1849 was the first to approach this in a scientific spirit. He suggested that the infective diseases generally might be parasitic in nature and a decade later Barnes, in the United States Army Reports, wrote that investigations into the malaria fever as seen in Fort Scott, Kansas, had added probability to the assumption. Thereafter, of course, there were several candidates for the honourable position of being the *causa causans* of malaria and the whole series constitutes an admirable illustration of Pasteur's dictum. Be very careful when you are looking for a thing, or you will be sure to find it.

First came Massy of Ceylon who recorded the finding of a microscopic fungus in the air where malaria was rife and said that it was precipitated everywhere, in the urine, and sputa of the sick, and was, he believed, the true malaria poison. Holden soon after studied a ship outbreak and found, as was not unlikely, *Thallophyta* in infected store-rooms. These, he said, were harmless *per se*, but when they combined with SH_2 from decaying vegetation and bad water [bilge] in the holds, they caused the disease.

Next came Van den Corput who stated that as a student he had often suffered from malaria while growing algæ and other plants in his bedroom. This, again, was quite probable, either as a coincidence merely, or from mosquitoes breeding in the water in which he grew his plants. The algæ idea was also taken up by Balestra who, however, went further, saying that he "took fever twice after drawing deep breaths over a vessel containing water from the Pontine Marshes of the Roman Campagna, in which algæ were present." In 1879 came Klebs and Tommasi Crudeli with their bacillus and this was held for some years to be the cause of malaria, persuading even so acute and far-seeing a man as Marchiafava. Their account is certainly very detailed and convincing. They found rods and oval motile spores which "when isolated and cultivated produced the most marked malarial sickness in the animals which received them." The form of disease produced varied from the very mild to the most severe pernicious type, proving fatal in twenty-four hours. In the animals so affected they found a melanæmia and a swollen spleen—"further evidence of the identity of these artificially produced fevers with the malarial sickness occurring in man." We may ask whether they were

dealing with *Bacillus anthracis*, for that would produce the effects detailed when injected into laboratory animals Marchiafava, however, found the same *B. malariae* in the bodies of several persons who died in Rome of pernicious malaria fever. It would help us to determine what organisms he found if we could know how long after death the autopsies were carried out and what pathological lesions he found. Anyway, Griffini reported that he was able to confirm their occurrence in cases in the Lombard rice-fields.

An organism for which properties so important were claimed calls for more notice. The bacillus of Klebs and Crudele was found by them in the soil of the Roman Campagna and, as recorded in Klein's *Micro-organisms and Disease*, it was 2-7 microns long and grew well when attempts at cultivation were made in albumen or glue, and other substances, multiplying by spores [perhaps it was *Bacillus mycoides*, a motile bacillus resembling *B. anthracis* morphologically and present in soil]. They named their organism *Schizometes bacillaris*, they inoculated rabbits with it and claimed that it produced in these animals 'intermittent fever' and enlargement of the spleen. They were of opinion that malaria, ague or intermittent fever was associated with exposure to exhalations from marshy ground, that certain organisms could be washed out from the soil of a fever-haunted marsh, that the organism isolated by them floated in the air which rested on the marsh, that by shaking up this air with water the organism could be washed out from the air, and finally that "the water thus infected when introduced into the circulation of a dog produced ague more or less rapidly according to the numbers in which the microbes were present."

The special danger of exposure at the time of sunset was accounted for as being due to the concurrence of three factors. First, concentration of microbes or spores a little above the ground. Over the surface of a dried-up marsh, it was maintained, there would be a condensation of these microbes, not being lifted by ascending air-currents, but beaten down to a lower level, and also to their viscous coherence the result of horizontal disposition of the air near the ground, as the earth cools by radiation, and of the instant deposition of vapour on the dust particles. Consequently, the microbes would gather in myriads about the height of a man's head, just as we see a ground fog when the air is warm and still at the end of a warm day in early autumn. Second, the dew condensing on the microbes would preserve their virulence. This is stated as an *obiter dictum*, no attempt is made to prove it.

Third, the rapid cooling of the human skin at sundown drives the blood to the interior of the body and particularly to the mucous membrane of the throat, and the congestion resulting would favour the inoculation of germs drawn in with the breath

Marchiafava seems to have had a sort of *arrière pensée* that this bacillus of malaria did not satisfy all requirements, for he and Celli reported that, having examined the blood of malaria patients, they found it "containing certain bodies, in size a fraction of that of the blood-discs" and that such blood would produce intermittent fever if injected intravenously into other human subjects

In spite of the discovery of the protozoon by Laveran in 1880, of which more will be said later, and of the enormous amount of work which had been done on it subsequently and the prodigious output of literature, the bacillary idea died hard. In 1898 Dr Dunley Owen stated in the *Lancet* that malaria was very prevalent in Rhodesia and that the poison was especially virulent one hour before and after sunrise. He went on to tell how he had made cultivation of the bacillus obtained at that time of the day from the grass and soil and up to a height of 4 feet above the ground level, but not higher. The horse-sickness of Rhodesia was also believed to be a form of malaria and the following is the explanation given. That horses stabled at night and not let out to graze before 9 or 10 a.m. did not fall sick, whereas those turned out at or before sunrise were almost sure to contract 'horse-sickness'.

Hirsch gives a good summary of the question which cannot be expressed better than in his own words (Sydenham Society's translation)

Whether we regard the malarious substance as a product of the decomposition of organic matters, or as parasites, or as an animal or vegetable poison. we shall always ascribe *specific* properties to it and always come, therefore, in the end to some specific source whence it has arisen. We are, therefore, driven to the supposition that the morbid poison develops only from, or within, certain organic matters (animal or vegetable), and so the inquiry directs itself in the first instance to the study of the lower fauna and flora both of the localities where malarial fevers are endemic, and also of those which are exempt from the disease, with a view to ascertaining from a comparison of the results so obtained, first of all what animal or vegetable forms the production of malaria appears to be associated with. It is not the *amount* of vegetation (which has hitherto so fixed the attention of enquirers) as the *specificity* of it which ought to come mostly into consideration.

Away down to 1880 medical textbooks described malaria as an earth-born poison or a miasm which emanates or is exhaled from certain soils, more particularly the soils of warm climates,

and causes the agues and remittent fevers known as malarial, and the following were enumerated as the ascertained Laws of Malaria

1 The malarious poison is extricated in greatest abundance in low, marshy and alluvial soils, though not confined to such situations [Extricated appears to be used in the chemical sense of 'released']

2 Malaria is extricated from all wet lands, the muddy surface of marshes and the slimy banks of lakes and rivers during what has been termed the drying process

3 Malaria is never extricated from the surface of water under any condition whatever, so long as the particles of the latter fluid hold together

We must confess that we do not quite grasp the meaning of this, but it would seem to mean that it is not the water itself, but the mist vapour, miasma over it and generated by or from it, that contains the poison

4 Malaria becomes innocuous at a certain distance from the source whence it is given out

5 The specific gravity of malaria is greater than that of atmospheric air, but winds of a higher temperature enable the heavy malarious gas to ascend to higher elevations than under ordinary circumstances

6 The interposition of a forest, a mountain, a wall, or even a mere cloth, is sometimes sufficient to preserve an individual, or individuals, from the pernicious effects of the miasmata given out on the opposite side

Umbrageous trees were believed to arrest the spread or neutralize the poisonous qualities of malaria. We have seen examples elsewhere of a belt of trees seeming to ward off malaria and their removal being followed by an increase of infection

7 Above a certain height all situations are free from endemic fever, not only in temperate but in tropical climates, although 'the line of perpetual health' will be higher in the latter than in the former

Much of the knowledge on which we pride ourselves as recently discovered is of the nature of re-discovery. It has been held for many years, two or three centuries perhaps, that natives suffered less from, or were even immune to, fevers which attacked the white man severely (see p 6) and we explain that by saying that the native suffers from repeated small infections which have produced a state of immunity, partial or total. But this is not new, though perhaps such a scientific method of expressing it is of more recent date. It was known a hundred years ago. Children of negroes in Senegambia were observed to suffer severely from malaria and the relative freedom of the black man in the Niger districts was acquired, and was not a congenital or racial trait. The predisposition was less in proportion to the degree of exposure

to which they had been subjected from birth to maturity without severe disease. In the Niger Expedition of 1841-2 it was noted that eleven of the fifty-eight negroes were attacked with fever and these eleven had lived for a long time in England and being away from their native country had lost their immunity, thus it was clear that no race or nationality was naturally immune.

We have now arrived at one of the most important milestones on the road of the history of malaria—the discovery of the causative protozoon by Laveran on 6th November, 1880.

Alphonse Laveran was born in 1845 in Paris and took his medical degree at Strasbourg in 1867 at the age of twenty-two years and became an army surgeon, and it was while he was stationed in Algeria that he made his momentous discovery of which we will speak in more detail shortly. He was not actually the first to notice the organism though to him is due the credit of grasping its significance. Eight years previously, in 1872, Delafield published a small volume which he called a *Handbook of Post-mortem Examinations and of Morbid Anatomy*, and which is of interest further as being the skeleton, the groundwork, on which Delafield and Prudden's *Textbook of Pathology* was built, published in 1885 and in 1936 reached its sixteenth edition. In his original *Handbook* Delafield wrote, under the heading 'Malarial Fevers'

We find the most constant lesion is the presence of little particles of black or reddish pigment in the blood. The pigment is in the form of flakes or of granules embedded in small, irregular, transparent, finely granular bodies. We also find the same transparent bodies without pigment.

What can these have been if not the malaria parasite? He did not, however, suspect its nature.

Prior even to Delafield was Heinrich Meckel who, as long ago as 1847 described pigment in the blood and organs of an insane patient who had died from malaria. He talks of "irregular granules, 0.002-0.007 of a line, united by a colourless substance to a globular, egg-shaped, or fusiform body." Virchow later confirmed his findings.

Laveran's discovery and its interpretation constitute an excellent example of what we may call 'Science and the Prepared Mind,' on which a very instructive essay might be written. On the 6th November, 1880, Laveran happened to be examining the blood of a malaria patient and was observing certain pigmented hyaline bodies when he saw several long flagella suddenly extrude

from them and lash about in the blood. He regarded these bodies as *Oscillaria* and called them *Oscillaria malariae*. In his work *Nature parasitaire des accidents de l'impaludisme, description d'un nouveau parasite trouvé dans le sang des malades atteints de fièvre palustre*, published in Paris in 1881, Laveran writes

Les filaments mobiles des corps n° 2 ont une grande analogie avec des *oscillariees*. Il est à noter que plusieurs observateurs, qui ne soupçonnaient pas l'existence de ces animalcules dans le sang des malades atteints de fièvre palustre, ont attribué déjà un grand rôle aux oscillariees dans la pathogénie de l'impaludisme. Hallier, le premier je crois, a émis cette opinion, toute théorique d'ailleurs.

Le Dr Schurtz de Zwickau cite le fait d'un homme pris de fièvre intermittente dans les conditions de salubrité très bonnes en apparence, ce malade se livrait à l'étude des cryptogames et il avait dans sa chambre à coucher vingt-quatre soucoupes renfermant des oscillariées (*Arch d'Helk*, 1868, p. 69). S'il était démontré que les filaments mobiles des corps n° 2 sont bien réellement de l'espèce des oscillariées, le nom d'*Oscillaria malariae* conviendrait bien au nouvel hématozoaire.

On the 23rd of the same month, November, he published a short note on these *Oscillaria* at a meeting of the Académie de Médecine, Paris, and made a second communication on the 28th December. In 1881 he issued a monograph with a detailed description of 'certain parasitic elements' in the blood of patients suffering from malaria, he found them in 148 out of 192 specimens of blood examined. His microscope gave a magnification of 400-500 diameters. In 1884 was published his *Traité des Fièvres palustres* and his larger work, *Paludisme*, eight years later when he was Professor of Medicine at Val de Grâce.

These announcements of 1880 and 1881 were confirmed by Richard who, at Laveran's suggestion, was studying the question at Philipville, Algiers. Laveran, in 1882, in a communication to the Paris Académie, had said that "the parasites in their early form present a small clear spot which grows and acquires pigment and later fills the corpuscle and in the end bursts it," in other words it is an endocorpuscular parasite. The same year he visited Rome and showed his preparations to the Italian malarialogists, Marchiafava and others, but they were sceptical, as at that time the Klebs-Tommasi Crudeli bacillus held the field and had their support. The filaments, they said, were only heat products of the red corpuscles. However, after seeing Laveran's specimens they reconsidered the question, examined more specimens for themselves, staining with methylene blue, and in 1884, when Laveran's *Traité des Fièvres palustres* came out, they gave their views, being still unconvinced, that the pigmented bodies indicated retrograde

changes in the corpuscles in which the hæmoglobin became transformed into melanin Marchiafava noticed that certain spots took up the stain and these spots he thought strongly resembled micrococci (we must bear in mind that in those days dry lenses only were in use) He attempted to grow these on culture media favourable for micrococci and as they failed to grow he decided that they did not belong to that group but were the result of degenerative changes in the cell plasma He then began to use an oil-immersion lens, Zeiss $\frac{1}{2}$ ", and in 1884 he recognized amœboid movement in the small hyaline unpigmented spot or body enclosed in the erythrocyte and knew that he was dealing with a parasite

It was not until 1912 that the parasite was artificially cultivated by C C Bass and F M Johns of the Tulane School of Tropical Medicine, New Orleans To save returning to this again we may give here a brief note on the method by which they attained success

Ten cubic centimetres of blood were taken from a vein and defibrinated, and to this 0.1 c.c. of a 50 per cent solution of dextrose was added Incubation was carried out at a temperature of 40–41° C in a tube containing a column of at least two inches in depth and with at least half an inch of serum above the corpuscles The parasites are to be found in the upper $\frac{1}{15}$ – $\frac{1}{20}$ " of the corpuscle layer For obtaining a second generation of parasites the leucocytes are removed by centrifuge, lest the extracorpuseular forms are destroyed, and the subculture has to be undertaken within six hours of sporulation The sexual stage is, of course, not obtained in the culture tubes

Confirmation of Marchiafava's findings soon began to be reported from different parts of the world by Sternberg in New York in 1886, by Osler in 1887, Maurel in Paris the same year, Sacharoff in 1889, Paltauf in Germany in 1890, Plehn the same year, and by Quincke in Schleswig-Holstein also in 1890

Though they were slow to be convinced even when the parasites were shown to them by Laveran, the Italians made up for it later by their discoveries from 1885 onwards, especially noteworthy are Marchiafava, Celli, Golgi, Canalis, Grassi, Feletti, Bignami, Bastianelli and San Felice

In the course of a few years differences of opinion on several points arose between Laveran and the Italian observers and the victory was not by any means always one-sided Thus, Laveran regarded the parasites as pigmented, at times adherent to the corpuscles [some maintain this at the present day], giving rise to motile filaments, these filaments representing the perfect form of the parasite after it acquires independent existence in the plasma In 1883–4 Marchiafava and Celli found that the pigment

was formed in the red cells after they had been invaded, the hæmoglobin being converted into melanin, they also stated that the filaments were flagella of a certain phase of the parasite's development. Two years later, in 1885-6, Golgi differentiated the parasite of tertian from that of quartan fever and showed this important clinical point, that the beginning of the febrile paroxysm is synchronous with the stage of sporulation of the parasite.

In 1889-90 Marchiafava and Celli, by researches carried out in the Roman Campagna, differentiated the milder spring forms of malaria, the tertian and quartan, from the summer-autumn type which might suddenly develop dangerous symptoms. Bignami in 1890 investigated the pathology of malaria and correlated the findings with the cerebral symptoms, especially the comatose variety. C. F. Craig and E. C. Faust in their well-known work on *Clinical Parasitology* (1937) state that

Ancient Chinese physicians differentiated tertian, quartan and æstivo-autumnal malaria on the basis of their febrile manifestations, and associated "ague-cake" with malaria, just as did the Greek and Roman physicians many centuries later.

Metchnikov in 1887 classified the parasite with *Coccidia* and gave it the name *Hæmatophyllum malaricæ* and Pfeiffer five years later indicated that the development of the coccidium in the rabbit and that of the malaria parasite bore a close resemblance. In 1897 W. G. MacCallum reported at a meeting of the British Association in August his observation of the mode of fertilization of the malaria parasite of birds and two months later he announced to the Johns Hopkins Medical Society that he found the same to hold good for the human parasites. He observed that shortly after the blood containing crescents is drawn these crescents become ovoid, then spherical and escape from the corpuscle. From some of these spheres, after 20-25 minutes, flagella are thrown out and, breaking away from the main body, approach other spheres which, however, are quiescent and do not extrude flagella. One flagellum was seen to penetrate a quiescent sphere and the pigment therein became forthwith violently agitated, the sphere swelled and again became quiescent.

Little useful purpose would be served by entering in any detail into the many discussions which took place as to the position of the malaria parasite in the zoological system. Among the suggestions advanced the following are the chief

Oscillaria malaricæ, suggested by Laveran, but later rejected by him
Hæmatozoon malaricæ (Laveran)
Hæmatophyllum malaricæ (Metchnikov)

Plasmodium malariae (Marchiafava and Celli)

Haematomonas malariae (Osler)

Haemamoeba malariae—for the quartan parasite

Haemamoeba vivax—the tertian parasite

Haemamoeba pigmentosa—the pigmented quotidian parasite

Haemamoeba immaculata—the unpigmented quotidian parasite

Laverania malariae—the crescent form (Grassi and Feletti)

Strange to say, the only one which has taken root and become permanently established is Marchiafava and Celli's term *Plasmodium* and that is, really, the least suitable. Its godparents intended it to apply to the small unpigmented amoeboid immature forms of summer fever, not to the spore-forming body or the crescent. Zoologists apply, or did apply, the term *Plasmodium* to the colony formed by conjunction of numerous *Amoeba*, each of which maintains its nucleus, i.e. a multinuclear protoplasmic mass. Anyway, it has now become established and we cannot alter it, nor, of course, the specific name *falciparum* for the subtertian parasite. The latter was given because of the sickle or crescentic shape of one stage in the life-history, the author of the name apparently being sufficient of a Latinist to know that adjectives in the neuter often ended in *-um*, but not sufficient to remember that 'par' does not change in the neuter and that *falciparum* would not be the nominative singular but the genitive plural.

We may, to avoid returning to the subject of the parasites themselves again, anticipate here by mentioning other forms which have been reported from time to time. In 1914 J. W. W. Stephens, examining a film of blood from an Indian child in the Central Provinces, found a parasite which he thought differed from the ordinary subtertian parasite in its amoeboid activity and the abundance and irregularity of its nuclear matter. He named it *Plasmodium tenue*, but Balfour and Wenyon showed that it was not a form distinct from *P. falciparum*. Apart from this, the name had already been pre-empted by Laveran for the parasite of a Japanese bird.

In 1914 Ahmed Emin at Camaran in the Red Sea saw and described a parasite which Stephens in 1922 also saw in smears from East Africa and in 1927 in another from Nigeria. This was named *P. ovale*, and it is almost certainly a distinct species, since its morphological peculiarities are retained on passage from one person to another. We must here state that *P. ovale* seems to have been first described, though not named, by Craig in 1909. Craig has called attention to this as claiming priority to Ahmed Emin (although Craig states that the plasmodium described by the latter was not identical with *P. ovale*). The parasite has

certain features in common with *P vivax* and *P malariae*, and produces a mild type of tertian fever

H M Smith described in 1905 what he believed to be a new form of parasite occurring in pernicious cases in the Philippines. He described them as "Refractive spindles, one to two-fifths the diameter of a red cell, with a dot of hæmoglobin in the middle, and staining with difficulty." This description and the illustrative pictures apply equally to clefts in the corpuscles seen in some preparations of normal blood.

In the same year, 1890, there was much discussion by Golgi, Angelini, Grassi, Feletti, and others on the significance and clinical importance of the crescent or semilunar bodies which Laveran was the first to describe.

Laveran, after much thought, refused to admit that there were any real, valid differences between the parasites of the different types of fever, although Grassi and Feletti had found that malignant infection was the result only of the summer-autumn (æstivo-autumnal) parasite, and would nearly always follow if the parasites were numerous or the injection contained parasites of two or more generations. Bignami in 1893, with Bastianelli, experimented in order to determine the period of incubation of the æstivo-autumnal type by inoculating blood containing the parasites. They established the important fact that positive results followed injection of blood containing young parasites, but that no fever resulted when blood containing only the crescent forms was inoculated.

Thioux, a French physician, working in West Africa supported Laveran's views regarding the unity of the malaria parasite, basing his opinion on the fact that if he examined native children—he was then in Senegal—in the hot season he found the 'tropical forms' in 98.5 per cent of cases and the 'tertian and quartan' in 1.5 per cent only, but in November and December the relative proportions were 73.5 and 26.4 per cent respectively, and in March and April 64.1 and 35.8 per cent. He considered it far-fetched and difficult to admit the existence of a summer and winter malaria due to absolutely different species.

The following is a summary of the main differences between the views of Laveran and those of the Italian school.

- 1 *The parasite itself* According to Laveran a motile filament, to the Italians a sphere which segments to form spores.
- 2 *Stages of growth of parasite* In early stage unpigmented, later becomes pigmented, according to Laveran, who merely states it as a fact and makes no attempt to

account for it The Italians followed out the development of pigment in the corpuscle

- 3 *Central pigment* Laveran regarded this as a cadaveric form of the parasite, the Italians considered it of great importance, as a prelude to sporulation
- 4 *Crescents* Laveran considered these as connected with chronic malaria and the existence of cachexia, the Italians showed that they were not met with in the spring forms of fever, but only in the æstivo-autumnal, and that fever does not result from inoculation of blood containing them, if parasites themselves are absent
- 5 *Varieties of parasite* Accidental and have no connection with any special type of fever (Laveran), each variety causes a special type of fever (Italians)
- 6 *Relation of parasite to corpuscle* According to Laveran the parasite is extra-corpuscular and often free, according to the Italians it is endoglobular except in the spore stage
- 7 *Causes of fever* Laveran is vague on this point, he ascribes it to accumulation in the blood of a secretion from the parasites or to a rapid multiplication of them The Italians stated that the actual time of the febrile paroxysm coincided with the liberation of spores from the corpuscles to become free in the plasma, and the proximate cause was possibly a secreted toxin
- 8 *Cause of type of fever* Also vague, according to Laveran who ascribes it to idiosyncrasy, or acclimatization, or the condition of the patient's nervous system, etc The Italians correlate the type of fever with the variety of parasite
- 9 *Cause of intermittence* Laveran thought that phagocytosis or substances liberated by the parasites inhibited production of other parasites, the Italian school explained it by saying that fever came again when spores were again liberated
- 10 *Cause of periodicity* Laveran offered no explanation, he thought that nothing definite could be stated, that diseases other than malaria might also show intermissions and periodicity The Italian explanation was that each variety of parasite has its own cycle of development This naturally would not appeal to a unicist who maintained that there was only one form of parasite

- 11 *Cause of recurring fevers* Laveran merely repeats that 'recurrence is the rule' and has no explanation to offer, the Italians accounted for it by saying that some of the spores escaped destruction and remained latent, perhaps in the spleen or bone-marrow, to re-enter the blood stream later
- 12 *Cause of quotidian fever* According to Laveran, no distinction, any of the fevers might become quotidian According to the Italians, double tertian (tertiana duplex) or triple quartan (quartana triplex) would result in quotidian fever
- 13 *Action of quinine* Laveran said that it killed the parasite or, short of that, prevented escape of the filaments The Italians held that it prevented the young parasites from entering the red corpuscles, also that it inhibited nutrition of the parasites, so, if given late, only the advanced forms would segment

This seems to be a convenient place to mention that when one reads the Italian works on malaria of the eighteenth, nineteenth and twentieth centuries one not infrequently meets with the words *solitaria* and *comitata* Torti uses them quite often The significance of these is not altogether clear, but from consideration of the context in each case we get the impression that the former is applied to the simple malignant (subtertian) fever and the latter to the same with complications The *solitaria* includes simple marsh fevers, whether intermittent or remittent, the bilious and gastric forms and the adynamic or typhoid form, as it used to be called *Comitata* would include those with choleraic or dysenteric symptoms and those with marked cerebral symptoms This is as near as we can get to the distinction—not very satisfying and largely a difference of degree of severity, since all are of the subtertian group

Another distinction not easy to interpret is that between *ricadute* and *recidivi*, often translated as 'relapses' and 'recurrences' respectively In the early days of the use of these terms infection was believed to come from the air (mal' aria), acquired by man through inhalation, and consequently parasites would naturally be present in man in different stages of development The series of paroxysms, or perhaps it would be more accurate to say the serial character of the paroxysms, is due to the evolution of a single generation of parasites, and the fever becomes irregular or complex (*ricadute*) because different generations mature at

different times, though each generation has its own periodicity—an overlapping of evolution or maturation times. When, however, an attack is over but all the 'spores' are not killed off certain of them lie latent, in the spleen and bone-marrow, as stated above, and their time of latency is the period of apyrexia. Later on these latent forms begin again to develop and when they reach a certain stage or number a *recidiva* or recurrence is brought about.

4 TRANSMISSION

Though actual proof that insects can act as transmitters of disease is of recent date, going back between fifty and sixty years only, the idea, in a vague shape it is true, existed long before that among the aborigines of India, Africa and South America, and, as regards the subject of this study—malaria—among the peasants of the Roman Campagna. Mention has been made that Varro in 36 B C and Columella in A D 100 spoke of the connection between marshes and fever and postulated organisms too small for naked-eye visibility as conveying the disease *viâ* mouth or nose, that is by being swallowed or inhaled. Columella went even further and remarked that marshes bred mosquitoes armed with stings and that these insects might convey disease by their bite (see p 141).

Long before they were found to be vectors of disease to man, predatory and parasitic insects were known in horticulture, for example, sugar-cane disease, scale insect in the mulberry cultivation and so on. Also a disease of camels which occurs in Algeria and is caused by a spirochæte was shown to be carried by gadflies which are themselves killed off by robber-flies. Our concern, however, is with human disease. Two hundred and twenty years ago Lancisi put forward a theory that organisms might be mosquito-borne and nearly a century ago Nott of Mobile, in 1848, when writing *On the Origin of Yellow Fever* in a paper published in the New Orleans Medical and Surgical Journal, refers to malaria as if the mosquito theory had already been advanced. Also Beauperthuy, in 1854, thought that mosquitoes were instrumental in carrying yellow fever and noted that malaria and yellow fever were absent where there were no *insectes tipulaires* (see later, Yellow Fever). The first actual proof, however, that insects could cause disease was made in 1879 when Patrick Manson demonstrated how the embryos of *Filaria bancrofti* (in early days *Filaria sanguinis hominis*, now *Wuchereria bancrofti*) are taken in with human blood by the *Culex* mosquito, how these embryos develop inside the insect and gain entrance through the puncture made when,

after this interval for development, the mosquito bites another human subject [The embryo is not injected simultaneously through the puncture in the way that the malaria parasite is] Ten years later Smith and Kilborne proved that Texan fever in cattle was transmitted by a tick Manson's discovery was not regarded as of much importance at the time, but it arose from this that nearly twenty years later (in 1897-8) Ross was able to show that the parasite of malaria was conveyed from man to man in a closely similar way—that the parasite went through a double life-cycle, sexual in the insect, asexual in man, and that malaria was no longer to be regarded as due to bad air or marsh exhalations, but was the result of a phase in the life-cycle of a known organism Great though the work was that Ross accomplished, we must not fall into the error which is by no means uncommon (Ross himself did not steer altogether clear of it at times) of attributing it all to Ross and his genius *de novo*, as if he had conceived the idea out of his inner consciousness, formulated a theory, worked at it and brought it to a successful issue We have seen that the 'mosquito theory' had been crystallizing out, as it were, for some time Apart from Columella's surmises at the beginning of the Christian era there is abundant evidence that for years, perhaps even for centuries, the idea in a hazy form was present to the minds of the peasants of the Agro Romano They would condemn as malarious any locality where mosquitoes were prevalent Again, shepherds coming back to the Agro from the Apennines would always smoke out the cabins in order to drive out mosquitoes before occupying them This was not merely for their own comfort and to prevent the nuisance of being bitten, for they would often house sheep in the cabins for some days before living in them themselves—a forestalling of what we now speak of as zoophily—in order that the mosquitoes might have a good preliminary feed on the animals before the peasants were subjected to their attack

Sir Henry Blake (quoted by Boyce) when he was Governor of Ceylon saw a medical work written in the sixth century in which the mosquito was said to be the carrier of disease and malaria was described as transmitted by flies or mosquitoes Unfortunately Blake does not give the reference or even the title of the book, nor does Sir Rubert Boyce when mentioning this It would be interesting to know how the writer of these early days described 'carrier of disease' and what was his term for 'malaria'

Professor Nuttall notes that the natives of Usambara Mountains (then German East Africa) were convinced that malaria

and mosquitoes were connected and that if the hill-dwellers left the mountains and came down to the lowlands they would contract the disease, and Ross in 1898 wrote that in parts of Africa and in Assam the natives believed that fever resulted from bites of mosquitoes. Professor Nuttall also states that Professor Koch informed him that the possibility of mosquitoes playing a rôle in transmission of malaria first occurred to him in India in 1883-4, ten years before Ross took up the question scientifically and that since then he had constantly spoken of it in his lectures, though the first reference found in medical literature to this is in Pfeiffer's article *Beitrag zur Protozoenforschung*, Berlin 1892, where the following occurs (p. 22)

Es ware möglich dass auch bei den Malariaparasiten exogene Zustände existiren Entwicklungszyklen, die ausserhalb des menschlichen Körpers, vielleicht im Leibe niederer Thiere (gewisser Insekten z. B.), vielleicht auch zum Theil mindestens im Boden sich abspielten. Diese exogenen Malariakeimen können dann durch die Luft, durch das Wasser, oder, worauf Robert Koch mich aufmerksam machte durch die Stichblutsaugende Insekten auf den Menschen ubertragen werden.

Manson first speaks of the probable relation in 1894, drawing an analogy between malaria and filariasis, he considered the flagellated form of the malaria parasite as the first phase in its extra-corporeal existence. Hence his constant advice to Ross—"Follow the flagellum."

The literature on the subject at the end of last century shows how the 'theory' had been discovered, or rather re-discovered, in different countries and originality claimed in each case, France ascribed it to Laveran in 1891, Germany to Koch and Pfeiffer in 1892, England to Manson in 1894, Italy to Bignami and Mendini in 1896, and, not to be outdone, or thinking perhaps that numbers would make up for loss of priority, to Grassi in 1898.

Let us carry ourselves back mentally to the last year of last century and review the evidence at the time relative to the mosquito-malaria theory, as given by Nuttall. He marshals it under certain main headings

1 *Nature of countries in which malaria prevailed* Low-lying, moist places with swamps, jungle, river estuaries, and valleys, especially after subsidence of inundations. Many examples of the last might be given, such as the Nile, Ganges, Indus, Euphrates and the Mississippi. Also low seaboard, pools and stagnant water, whether natural or artificial as by irrigation without proper drainage.

2 *Season of the year* Warm and moist seasons which are also most suitable for the breeding of mosquitoes.

3 *Conditions generally considered to protect against malaria*
 These were the same as those which protect against mosquitoes
 The presence of woods by obstructing transmission by winds As
 examples the following may be quoted

(a) In 1826 there was an outbreak in Alabama A large farm on which 150 persons lived in good health was situated half a mile from a swampy lake, between which and the farm was a dense wood This was cut down and all but three or four of the dwellers on the farm were attacked by malaria

(b) A plantation was situated a quarter of a mile from a creek, but separated from it by a thick wood In 1842-3 this was cut down and the negroes working on the plantation, who had previously enjoyed the best of health, were severely attacked

(c) It has been again and again reported (*e g Lancet*, 1878, II, 683) that Assam tea-gardens became unhealthy when virgin forest was cleared away, and that in Borneo the clearings are unhealthy and malarious, but protection is gained by leaving forest standing on the windward side of clearings

Though collections of water are dangerous as affording breeding places for mosquitoes, a *body of water* intervening in the course of winds from a malarial centre acts, like a wood, as a protection Thus, ships anchored at a distance off-shore were freer than those close in Sir John Pringle in his work *Observations on the Diseases of the Army in Camp and Garrison*, 1752, states that the British Army in Holland in 1747 suffered to such an extent from malaria that some battalions were reduced to one-seventh of their strength, while a squadron anchored in a canal between Zuit-Beveland and the Island of Walcheren was free of fever Rattray says of Hong Kong in 1839

The fever fatally prevalent on shore, the ships in the harbour, even when lying at a very short distance from the shore [the water there is often rough, not permitting oviposition by the mosquitoes, also it is salt and the malaria mosquito there is not a salt-water breeder] are usually exempt from its ravages

Vincent and Burot (*Acad de Médecine*, April 1896), speaking of Madagascar in 1896, relate that the soldiers in the expedition were attacked while the sailors on the men-o'-war or merchant vessels, in spite of great fatigue, remained unaffected Some ships stayed at an anchorage 300 metres out from the shore for as long as six months, only those men who were sent up the river and had to sleep on the ground were attacked by fever

4 *Personal protective measures* against malaria were also those that kept away mosquitoes Among these were Closing doors and windows or gun-ports at night [Lind, as we have seen, specifically recommended this], the use of mosquito-nets, gauze

veils and curtains This is mentioned by many, among them J Johnson in 1818, Macculloch in 1827, Brocchi in 1834, W J Evans in 1837 C F Oldham in 1871 speaks of the Jeevas of the Punjab fishing all night in the marshes and catching fowl, but nevertheless remaining unharmed in the midst of malaria because they changed at sunset into a costume which completely enveloped them Cretan fishermen, also, sleep with their nets folded several times round them so that they are entirely covered Yet Koch in 1898 advised the use of nets, screens and curtains and seems to take credit as if it were a new and original suggestion

5 *Cultivation of the soil* does good by removing or draining swamps or, perhaps, by changing the character of the vegetation [If, however, pools are left or holes made by borrow-pits in which mosquitoes can breed, the malaria is unaffected The fact was known that mosquito-breeding took place more especially in small pools or at the edges of marshes, swamps, or large areas of water, and hence the danger, which was both real and believed, of dredging a harbour or a river-bar, constructing a new road, turning up old soil, as 'sure to lead to an outbreak,' and indeed it often did and the new arrival would suffer from 'acclimatization' or 'salting' fever Similarly on ships, bilge-water, ballast and certain cargo favoured mosquito-breeding and fever]

6 *Flooding of the land* This has already been exemplified, complete flooding, in place of leaving pools or ditches, may be as effective as draining Thus, when the water stagnates or is drying up on rice-fields, breeding places for mosquitoes are formed, but when they are flooded and the water is circulating there is no malaria

7 *Avoidance of exposure after sunset*, when mosquitoes are most voracious

8 *Use of fires and smoke* Partly because they produce currents of air, partly because, if placed between the people and an open door, the mosquitoes are killed before they can reach the former Lind recommended the use of fires at sunset on ships near the shore in malarious districts

9 *Atmosphere and occupation* were shown to play a part in Zephyria, near Milo (Greece) Here there were sulphur deposits and the workers enjoyed good health, but when the workings were stopped malaria resulted in practically depopulating Zephyria

In 1883 King brought forward a strong plea that mosquitoes were the vectors of malaria, he founded his opinion on nineteen grounds which he adduced These need not be recounted here

The search for the mode of infection of malaria bears many points of resemblance to a modern treasure-hunt—vague early clues gradually narrowing the scope and defining the issue. In 1892 Pfeiffer, as we have said, pointed out the resemblance between the development of the coccidium in the rabbit and that of the malaria parasite, and Koch, who had followed Manson's work on the transmission of Filariasis by *Culex*, suggested to Pfeiffer that analogously infection might occur by the sting or bite of an insect.

Enough has been said to prove that the mosquito-malaria theory, in so far as it implied that mosquitoes and malaria were closely connected, the latter ætiologically with the former, was no new development in the time of Manson and Ross. The finding of the parasite gave investigators something tangible to work on in place of a vague miasmatic surmise. The next point to arise was, logically, this: Granted that there is a connection how does man become infected? In 1898 Manson, and also Laveran, there is no doubt, believed that this might occur through man drinking water in which mosquitoes had died after having fed on the blood of a malarial subject, or by inhalation of dust from pools which had harboured the parasite and dried up. As an inference from the former of these, many authorities recommended that drinking water should be boiled, as a prophylactic measure against malaria. Though King, Bignami, Mendini, Koch and Laveran (who believed in this as well as the imbibition idea) were of the opinion that infection was acquired through the *bite* of the mosquito, Manson still held that such a mode, if it occurred, did so only exceptionally.

Next came the idea of a distinction between what we now call 'mechanical transmission' and transmission by an insect acting as an 'intermediate host'. By the former, infecting material, *e.g.* in a patient's blood, is sucked up and within a short period is injected again into another subject, by the latter we understand that a certain period must elapse during which the infectious organism, *e.g.* the malaria parasite, trypanosome, virus of yellow fever, larva of helminth, undergoes certain stages of development and not until this has occurred does the insect—the intermediate host between donor and receptor patients—become infective.

That the former was, to say the least, improbable was generally held because, as one authority who may be quoted from several writes

The view that the mosquito carried the infection from man to man directly is untenable, if this were so infection would be much more frequent. We are forced to the conclusion that the mosquito must

be the *intermediary host* of the malarial parasite. If the insect gives rise to malaria through its bite, then the parasite must be given off in the mosquito's salivary secretion when it is sucking blood.

Both Manson (in his Goulstonian Lectures, 1896) and Laveran (*Comment prend-on le paludisme ? Rev d'Hyg*, 1896) express the belief that man may introduce malaria into a country by—himself infected—infecting the local mosquitoes and the disease may then become endemic. Lacaze's statement is in favour of this. He says in 1872 that malaria had existed in Mauritius for about three years before the first cases began to occur in the island of Réunion, though mosquitoes abounded in both.

We now come to the actual experimental work by which the mosquito-malaria theory came to be removed from the realm of theory to that of fact. Let us recall one or two important dates. In 1880 Alphonse Laveran discovered the parasite, six years later, 1886–7, Danilewsky discovered the corresponding parasite of birds. Meanwhile in 1885, Golgi observed multiplication of the parasite by the ordinary asexual process of spore formation and that the host's—the human patient's—temperature rises when these spores are liberated. He also showed that the tertian and quartan parasites were not the same. It was in 1889 that Ronald Ross, after studying malaria in Bangalore, found himself unable to confirm Laveran's discovery of the parasite and it was not until 1894, when he was shown the parasite by Manson when he was home on leave in London, that he became converted. In 1897 W. G. MacCallum published his account showing the true function of the flagella in the developmental cycle of the plasmodium.

The mosquito theory of Manson was

not a weak hypothesis framed on doubtful coincidences and analogies which had hitherto held the field, but a true scientific induction based on his sagacious interpretation of certain phenomena in the life-history of the parasite of malaria itself.

The theory may be stated briefly thus. Manson fixed his attention on the gametocyte and, noting that extrusion of motile filaments, or flagella, took place only after the blood had been withdrawn from the human host, he concluded that this extrusion, or exflagellation, is a natural organic process in the life-history of the parasite with a view to its further development in some suctional insect. The sporocytes, he said, continue the life of the parasites within the first host, man, bird [but as it has proved since, man is the intermediate host, *i.e.* the host in which the asexual development occurs], the gametocytes continue the

development within a second host [really the definitive host, in which the sexual development takes place], the suctorial insect Manson may be said to have thus combined and perfected in his final theory the previous hypotheses of King, Laveran and Mannaberg

Ross on his return to India took up the problem with enthusiasm and in 1897, in Secunderabad, in the course of examination of the stomachs of mosquitoes, found certain cells containing pigment granules and he sent a report to the Director-General of the Indian Medical Service on *Some Peculiar Pigmented Cells found in two Mosquitoes fed on Malarial Blood*. They appeared, he said, four to five days after the feed and were 12–16 microns in breadth. Ross had examined previously more than a thousand mosquitoes with negative results and their presence in these two led him to suppose that he had at last found the right species to serve as host. From 1895 he systematically examined mosquitoes to try to trace what occurred after they had sucked the blood of a malarious subject. Among them were several species of 'brindled' mosquitoes, two of grey, and a few with spotted wings. He employed natives to collect larvæ of all sorts which he kept in separate bottles and when the adults emerged they also were kept separately and allowed to feed on malarious patients. None of the 'brindled' or 'grey' specimens did he find infected, but on examining his last two he was rewarded by finding oocysts in the stomach wall, and he observed that, when the parent cell (oocyst) ruptured, the spores, as he called them (now sporozoites), poured into the body cavity of the insect and some gained entry to the salivary gland. In one mosquito there were twelve of these oocysts after four days, and in the other twenty-one after five days.

The following year MacCallum of Johns Hopkins University explained the function of the flagellum as an impregnator of the "pigmented spheres" (crescents, macrogametocytes) and Manson noted the next stage in the mosquito and called it the "travelling vermicule" or little worm, 'travelling' because of its spontaneous passage from the interior of the mosquito's stomach to the exterior. We see here Manson's helminthological bent interpreting this finding on the same lines as his *Filaria* discoveries.

In 1898 Ross was sent to Calcutta and tried to continue his investigations. Human malaria, however, was not common, so he turned to avian malaria and traced its life-cycle in *Culex* or 'grey mosquitoes'. He sent some of his specimens to Laveran who in June 1898 wrote as follows to Manson

It appears to me undoubted that the elements discovered by Dr Ross in the stomachs of mosquitoes fed on the blood of birds, subjects of hæmosporidiosis, are really parasites and that these parasites represent one of the phases of the evolution of the hæmatozoon. It is probable that it will now be easy to find the extracorporeal form (*la forme de résistance*) of the parasites in external media. The discovery of Dr Ross appears to me, as to you, to be of great importance, it is a great step forward in the study of the evolution of the hæmatozoon of birds and very probably also in that of the hæmatozoon of malaria.

Ross allowed 245 of his 'grey' mosquitoes (*Culex*) to feed on birds infected with *Proteosoma*, 178 or 72 per cent of them were later found to contain the pigmented cells, or oocysts. He also fed 249 of them on men whose blood contained crescents, but none developed the pigmented cells, i.e. the *Culex* served for development of the parasite of avian malaria but not for that of human. Continuing his work he examined a developed oocyst (now advanced to the stage we designate 'sporocyst') and found enormous numbers of minute slightly flattened spindle-shaped bodies which he called 'germinal rods' (now sporozoites) and these were present in the salivary glands later. He concluded that infection results from the bites of mosquitoes whose salivary glands contain these germinal rods.

The 'dapple-winged' mosquito (*Anopheles maculipennis*) to which he attributed transmission of human malaria he found in nature breeding only, or mainly, in small puddles caused by rains, in which no fish or frogs were present, and he claims that this explains the distribution of æstivo-autumnal malaria in India and its dependence on the rainy season. Hence for prophylaxis he advised (in addition to the use of mosquito-nets) measures directed against 'mosquito nurseries,' puddles, ponds, cisterns, and the like, especially near dwellings.

As ill-luck would have it he was now sent off to Assam to study kala azar, and Italian workers, especially Grassi and Bignami, took up the study and verified the discovery for human malaria and *Anopheles* on the same lines as Ross had done for avian malaria and *Culex*.

In 1898 Grassi, in an article by the title *La malaria propagata per mezzo di peculiari insetti*, recorded that in Italy and Sicily there were many places where mosquitoes were numerous but no malaria occurred. This, he thought, was probably due to the fact that the species present was not one of those suitable to act as host. [It might also be due, though he does not say so, to the fact that, if the species were suitable, no carrying cases had been introduced into the localities in question.]

Bignami was a believer in the mosquito transmission, but he thought that the insects acquired the specific parasite from the soil—marshy places, for example—and inoculated them into human beings by their bite. He was at one also with other Italian investigators in regarding the flagella of the parasite as products of disintegration, not as playing a fundamental part in reproduction.

Grassi and Bignami then collected a number of mosquitoes, mainly *A. claviger*, at Maccarese, a malarious focus some twenty-two miles from Rome on the Civita Vecchia Road. These were allowed to bite a patient who had been an inmate of the Santo Spirito Hospital at Rome, but who had never previously suffered from malaria. He became infected and his case was published by Bignami in the Bulletin of the Royal Academy of Medicine at Rome in 1898-9 in a paper entitled *Como si prendono le febbri malariche* [the same title as that of Laveran's (without the query mark) published in 1896, see p 165]. Since malaria existed at Rome, the experiment carried out on similar lines by Manson in 1900 is of greater value. Manson had some *Anopheles* which had been permitted to bite a malarious patient in Rome sent to England and these, after a suitable interval, were allowed to bite his son, Thurburn Manson, who in due course developed malaria.

In 1898 also, Grassi, Bignami and Bastianelli, in an article with the title *Ulteriori ricerche sul ciclo parassiti malarici umani nel corpo de zanzarone*, reported that they had examined (a) mosquitoes caught in rooms and cabins where malarious subjects slept, (b) some caught in stables and chicken-houses, (c) *Anopheles* at stated intervals after being permitted to suck the blood of malaria patients in hospital, (d) others after feeding on non-malarious patients. They found that 75 per cent of those caught in rooms and cabins contained the parasites, none of those in stables and outhouses, and that development of the parasite could be observed in group (c), but not in those which had bitten non-malarious patients. Thus the Italians were able to confirm Ross's findings in every particular and to advance them, and in 1898 there was formed an Italian Society for the Study of Malaria to consider and discuss the medical, sociological and preventive aspects of the infection. Thus the Italians, by applying to human malaria the principles which Ross had worked out for birds, were able to demonstrate clearly the transmission of the human parasite by *Anopheles*. Bastianelli, Bignami and Grassi in the same year, 1898, observed the complete development of the malignant, subtertian or æstivo-autumnal, parasite in *A. claviger* (*A. maculipennis*) and the following year that of the quartan parasite, and Bastianelli

and Bignami that of the benign tertian parasite in the same and, later, in other species. Confirmation soon was obtained from other countries. In 1899 Ross observed development of the quartan parasite in mosquitoes in Sierra Leone and the following year Ziemann confirmed the tertian and subtertian in *Anopheles* in the Cameroons, and van der Scheer and van Berlekom the benign tertian in *A. claviger* in Holland. The same year, 1900, appeared Grassi's illustrated monograph showing the complete life-cycles of the human parasites in *Anopheles* and he pointed out the importance of this type of mosquito in the epidemiology of malaria (Wenyon, C M, *Protozoology*, Vol II, p 911).

Soon after Ross's work in India became known the Right Honourable Joseph Chamberlain requested the Royal Society to appoint a Committee to co-operate with officials of the Colonial Office in the investigation of the causes of malaria and the possibility of controlling that scourge in tropical lands. The Malaria Commission of the Royal Society included C W Daniels, J W W Stephens and S R Christophers. It accomplished much useful work in the study of the disease in British Central Africa before it ceased to function in 1902. Daniels unfortunately had an attack of blackwater fever and had to return to England where he later became the first Director of the London School of Tropical Medicine.

As one of the results of the Commission's activities collections were made of the mosquitoes from different parts of the world and Theobald's work, *A Monograph of the Culicidæ*, was the outcome—a truly colossal work in size and importance, three volumes were issued in 1901 and one each in 1903, 1907 and 1910. In speaking of the enormous value of Theobald's publication, we must not forget the work of Major G M Giles which preceded it. This appeared in 1900 under the title *Handbook of the Gnats or Mosquitoes* and the second edition was issued in 1902.

Although the proving of the theory seems so crystal clear to us to-day it was not received without certain misgivings at the time. One or two only of the controversial points can be referred to here. In October 1898, in a paper published in *Janus*, Amsterdam, with the title *The Malaria Problem in the Light of Epidemiology*, A Davidson asked how far the mosquito hypothesis could be brought to harmonize with certain epidemiological facts which he adduced, six of them were puzzling.

- 1 Why should malaria break out in consequence of disturbance of the soil? We know now that this is due to the production of puddles where mosquitoes can

breed, and the introduction of labourers suffering from, or carriers of, malaria

- 2 Invasion of countries and districts previously free from infection This is explained by importation of infection by man or mosquitoes, in ships, by railways, later by aeroplane If by man the suitable mosquito may be already present, or one already there may adapt itself
- 3 The corollary of the last extinction of malaria in countries where it previously was prevalent This can be accounted for by changes of soil, drainage, moisture, vegetation, protection against mosquitoes, treatment of patients and preventive measures generally This is exemplified in the Lincolnshire fens, in Holland, in France and parts of Tuscany Though the *Anopheles* remain it is thought that drainage probably thins the number of them so that infection is mild, while the improved health of the inhabitants increases their resistance to infection
- 4 Occurrence of local outbreaks when marshy foci are made artificially This presents no difficulty in view of what has already been said
- 5 Presence of malaria in ships Given a malarious patient or infected *Anopheles* on board there was abundant opportunity in the bilge and water-casks for insect breeding
- 6 Presence of the disease at a season of the year when the temperature is low and insect life generally in abeyance This has presented a certain degree of difficulty, but houses are warmed and insects can hibernate in cellars Mosquitoes occur even in Arctic regions, in the Western Urals their appearance after hibernation is at first hailed with joy as the harbinger of spring, but the joy grows less as the days grow warmer and they wear out their welcome

Soon after this Christophers and Stephens recorded a fact of great epidemiological importance, that in malarious districts many natives, children especially, harboured the parasite without showing any symptoms, at all events without any suffering, they were, in fact, healthy or comparatively healthy carriers, in other words, the indigenous population is the reservoir of the parasite and the source of infection of the mosquito which breeds in small collections of water nearby and these insects after an interval for development infect the new arrival, the non-immune

Of passing interest historically is the question of the names

given to the stages of development of the malaria parasite. We now term the male cell the microgametocyte and the female the macrogametocyte, the male and female elements the micro- and macrogametes. These last were terms used in the study of lower plants and animals for spermatozoid, antherozoid, ovum and ovule. Ray Lankester who, as we all know, wrote among other things a book, *Science from an Easy Chair*, suggested in a paper to the Royal Society the following

- 1 For the needle-shaped, or spindle-shaped bodies injected by the mosquito into man, the term exotospore. Ross called them 'germinal rods' and the modern term is sporozoites
- 2 In man's corpuscles this exotospore (sporozoite) becomes amœbiform, hence Amœbula was suggested, now Plasmodium (trophozoite stage)
- 3 This breaks up into spores (modern term schizogony) or, as suggested by Ray Lankester, enhæmospores (now merozoites)
- 4 Some go on to form crescents (now gametocytes)
- 5 In the mosquito the spermatozoon (now flagellum, male gamete, or microgamete) develops from the 'sperm mother-cell' (male or microgametocyte), the corresponding female body being the 'egg-cell' (female or macrogametocyte)
- 6 By union of these, or fertilization of the latter by the former, a zygote is formed, which, because of its vermiform shape was called the vermicle (now ookinete)
- 7 Passing to the body-cavity aspect of the mosquito's stomach it becomes spherical, a cyst or sporecyst (now oocyst) and the contents break up so that the cyst becomes a 'spore mother cell' (now sporocyst) and the contents, as stated above, when extruded from bursting of the cyst, the exotospores

We have seen that one of the obstacles to the general acceptance of the mosquito-malaria theory was the fact that in certain districts formerly highly malarious the disease disappeared to a great extent, perhaps completely, although mosquitoes and the special malaria-carrying mosquitoes, Anophelines, remained. In other words what was the explanation for anophelism without malaria? The question cannot be said even yet to be entirely cleared up.

Celli and Gasbarrini in *Policlinico*, as long ago as 1901, stated that in certain parts of Tuscany—the swamps of Fucecchio and

Bientina, the Lago di Massaciuccoli and the marshes around it, and the Tuscan littoral from Collisalveti and Leghorn to Viarregio and Pietrasanta—malaria, once very prevalent, had practically disappeared. This was not ascribable to absence of *Anopheles*, for breeding-places were numerous and swarmed with larvæ and adults. It was not due to absence of infective sources for many persons returned there from malarious districts and examination of their blood showed the parasites, nevertheless the disease did not spread in the districts named. No explanation was offered, there was the bare statement that in Italy, as in England, France and Germany and parts of Holland, many districts previously malarious have ceased to be the habitat of the parasite. In England at least agriculture, drainage and improved sanitation generally have played a large part. The establishment of industries and laying out of plantations certainly take a share. Thus Sumatra was originally a place of marshy jungle and swamps where malaria was rife. Tobacco planting was started and as the plantations developed careful drainage was needed to obtain a good crop, together with suitable drying of the soil, swamps disappeared and with them malaria. Again, in Grenada, when sugar-cane was the staple product malaria was common, later cocoa replaced the cane and good drainage was needed, malaria lessened.

In the foregoing examples the explanation is not far to seek, but at times the phenomenon is not to be so easily accounted for. There are a number of districts in the neighbourhood of Amsterdam harbouring *Anophelines*, in some of these malaria is more or less frequent, in others it does not occur. Can the distribution be explained by biological differences of the insect vectors, or by variation in mere numbers, or, again, by varying access to human beings? There are two forms of *A. maculipennis* (perhaps more), the small-winged which does not hibernate is specially characteristic of the malarious regions. This is held to be an important factor of differentiation but not the sole factor, because this form occurs also in malaria-free regions. Ancillary factors are variations of gross population and of alternative hosts (animals).

Again, in the United States of America, in a district sixty miles north of St. Louis (Louisiana) malaria was once rife, but recent examination of school-children failed to reveal a single case, though *Anopheles* abounds. Rice cultivation was started there about five years before and was followed by marked increase of *Anopheles*, showing that the absence of malaria could not be

ascribed to decrease of vector Osler, speaking of malaria in the districts about the western end of Lake Ontario and the northern shores of Lake Erie, states "The marshes are still there and the Anopheles are there, but the disease has gone As in parts of Italy the important factor appears to have been the cinchonizing of the inhabitants" Disappearance was hastened, if this is the case, by cheapening of the drug

Again, some species of Anopheles are carriers, others are not, and, more puzzling still, a given species is a carrier in one place and not in another Thus, Winoto recorded 7 per cent of *A aconitus* infected among those captured in Western Java but, according to Swellengrebel, none of this species was found infected in Sumatra *A ludlowi* carries malaria in some regions, e g the mangrove swamps of Batavia and Singapore, but is harmless in the fishponds of Manila This is ascribed to the mosquitoes having different habits in different places, some being man-eaters, others not But this is mere tautology, it is no explanation Another example may be quoted Of *A maculipennis* caught in the delta of the Tiber 25 per cent were found in bedrooms and had bitten man, but in Massarosa (Tuscany), though the same species was very plentiful, only one out of 400 examined had bitten man

The subject is difficult and at present obscure Increase in the prosperity of those living in malarious regions has again and again led to decrease in the malaria Several factors have probably contributed to this In places of high endemicity the people are often impoverished, badly housed and insufficiently treated Domestic animals help in some places, by zoophily, but there is no definite evidence of this in the United States We do not know whether the malaria parasites have become less virulent New human carriers come into the northern states but only minor or transient outbreaks occur and the danger seems to be relatively small even though Anopheles are in considerable numbers and the decrease has come about without any conscious human aid It had nearly gone by the time mosquito-transmission was proved at the end of last century and Barber ascribes the diminution in the south and the north to the development of the country Examples are fairly plentiful of diminution of malaria when social conditions improve, in spite of the presence of Anopheles

Similarly, S P James has shown that the decline in England is not due to disappearance of the vector, *A maculipennis*, for this is still more abundant in many districts where malaria does not spread than in those where it does In England we find

three species of *Anopheles* *A. maculipennis*, *A. bifurcatus* and *A. plumbeus*, all infectable in the laboratory, but only the first in nature, because it alone lives in close association with man, in houses and cowsheds, especially the latter, not because of a preference for animal blood (as Roubaud suggests) but because it prefers darkness, moisture and warmth. Diminution of local malaria in England is not due to reasoned application of specific anti-malaria measures, but to progressive improvements of a social, economic, educational, medical and public health character. As Colonel James has said *A. maculipennis* is parasitic on man in proportion as human habits and mode of life are primitive and like those of the indigenous inhabitants of undeveloped countries where all the members of a family live huddled together in a cave, or in a windowless hut of mud or straw. In England during the last seventy years economic and social changes have been great. Houses are better lighted and ventilated, more open, less crowded, and less likely to harbour mosquitoes. Malaria persists in England only in a few isolated rural areas notoriously backward in amenities of modern civilized life—wages low, families crowded in dilapidated shacks. Special measures are called for when malaria affects those living under modern health conditions, but among the poor, illiterate, underfed peasantry living in dwellings more like those of primitive man, general improvement, bonification must take first place.

Bonification and drainage are at best only a partial explanation and in some places do not account at all for the presence of *Anopheles* and absence of malaria. Only a short time after the mosquito-malaria theory was promulgated it was noticed that the distribution of mosquitoes did not coincide in all cases with incidence of malaria and the theory was thought to have broken down. Its prestige was restored by the discovery of Grassi that only *Anopheles* carried the infection and others did not. The theory received another blow when Christophers and Stephens found that in certain parts of India there was no malaria though *Anopheles* were abundant, and in other parts there was much malaria though *Anopheles* were few. Further investigation, however, showed that though there were many species of *Anopheles* all did not act as vectors, where *Anopheles* swarmed but malaria was absent the prevailing mosquito was *A. rossii*, where *Anopheles* were few but malaria common *A. listoni* was the transmitter. The theory was again restored to its feet and able to stand upright. The conclusion to be drawn from this may be mentioned now (though it will be referred to again) that when preventive measures

are to be undertaken a preliminary is to find out which of the locally prevalent mosquitoes is the actual carrier in order that steps may be taken to deal with that. To attempt, as is done sometimes, or rather was—we are wiser now—to get rid of all mosquitoes is not only very costly, but is probably not even possible and certainly not necessary. This is what is known as 'species sanitation'.

Again, absence of malaria from certain parts of the globe—Barbados, Seychelles, Rodriguez and the Fiji group—cannot altogether be explained by absence of *Anopheles*, for there must be some reason why ship-borne *Anopheles* do not gain a footing. Barbados with its epidemic in 1927 is an example of the breaking down of this immunity (*A. albimanus* having been introduced). On the other hand, there are places where *Anopheles* are present yet malaria is absent, though there are highly malarious tracts in the neighbourhood. Tahiti, Hawaii, Samoa are examples of islands where *Anopheles* are not found and malaria is absent, while in the near-by Solomon Islands and New Hebrides *Anopheles* are abundant and malaria common. Mauritius and Réunion were exempt until *A. gambiae* was introduced from Africa, as mentioned already when we described the epidemic in Mauritius in 1866.

In Northern Australia five species of *Anopheles* are found and there was at one time considerable alarm that malaria might become widespread. These fears, however, are hardly justifiable because in urban areas where the population density is high mosquitoes are few and in the rural districts the population is sparse and scattered. Infection depends on several factors: the average population, the numbers of infected persons, and of these the proportion whose blood contains sufficient gametocytes to infect the local *Anophelines*, i.e. the intensity of the source, the number of *Anopheles* and the proportion of those which feed on infected persons, the numbers of those which so feed and survive for a week or more, and, lastly, the proportion of these which bite fresh human beings. These points have been calculated in general terms by Ross, as follows: 25 per cent of *Anopheles* present succeed in biting human beings [this, of course, is an arbitrary estimate and depends on several factors, some mosquitoes being zoophilous in preference to feeding on man, if there is an option], 8 per cent, or one-third of these will survive for a week and 2 per cent will bite a second person. In other words, about one in fifty *Anopheles* is likely to transmit the infection—clearly not a grave menace in Northern Australia.

Cases have been reported since 1923 in the Valley of the Lys, a temperate zone, where *Anopheles* is not rare. In this case Russian workmen were brought into France and they were harbouring the malaria parasite in their blood.

Details of the work carried out in India by Ross and the part played by Manson in making the results of Ross's work known and converting the theory into fact are given in a separate section. The main outlines have already been sketched and we can continue the history of malaria from the time of Ross's return to England from India in March 1899.

In the following month, on 22nd April, 1899, the Liverpool School of Tropical Medicine was formally opened by Lord Lister, the then President of the Royal Society. Three months later Ross went out to Freetown, the capital of Sierra Leone, with Dr H. E. Annett, Demonstrator of Tropical Pathology at Liverpool, and Mr E. E. Austen of the British Museum, Natural History. They found a serious outbreak of malaria at Wilberforce barracks among coloured troops brought from Barbados. It will be remembered that Barbados was one of those places free from malaria and these troops were, therefore, non-immunes, or, since it is a debatable point whether there is such a thing as immunity to malaria, we should say 'unsalted'. They found the walls of the barracks dotted with engorged mosquitoes, *A. gambiae* (*costalis*), 25 per cent (twenty-seven out of 109) of them infected, and in the patients' blood all three forms of the parasite. Ross reports on his attempts to carry out tests that the

authorities refused to allow me to feed any more of their valuable mosquitoes on their infected troops, apparently they were taking no precautions at all to prevent their soldiers from becoming infected from their mosquitoes, but strongly objected to their poor mosquitoes becoming infected from their soldiers.

Local search for breeding-places revealed that *Culex* was breeding in tubs and pots containing water, *Anopheles* in puddles and pools on the ground. These last were fed by runnels of water, passing over flat surfaces of rock or over soil with small hollows. These were not so small as to dry up readily or be scoured out by heavy rainfall, they were, many of them, permanent collections, containing masses of algæ and anopheline larvæ in large numbers. Other deposits of water resulted from railway construction works. Together there were abundant reasons to explain the Freetown outbreak. The first measure undertaken was the mapping out of these *Anopheles*-containing pools over the town, followed by either filling with cement, or, if too large for that, by oiling

Advice was given to the Freetown authorities and suggestions for eradication and prevention and in consequence the corporation appointed "a native on a salary of one pound a month, in order to cure the White Man's Grave of its evil reputation," as Ross put it in his typical way [Ross was a man who spent a good deal of his otherwise useful life in grumbling] Authorities, he says, deprecated expenditure, not recognizing that sanitary expenditure is an insurance against the much greater expenditure caused by sickness, as that of fire-engines against fire

In 1901 he again visited Freetown in order to give an object lesson in mosquito elimination A 'Culex gang' was formed to collect broken bottles, pots, empty tins—anything, in fact, which might become serviceable for mosquito-breeding, and an 'Anopheles gang' to drain or fill in puddles in streets or yards of houses Though marshes and swamps were receiving attention, being drained or filled, the small rain-pools near the houses were quite neglected "Many of the streets were practically marshes in the rains, the houses being situated in the midst of seething puddles full of mosquito larvæ," and, again, speaking of drains,

It was very largely these drains which were responsible for the bad sanitary reputation of the "White Man's Grave," many of them being huge square trenches without any adequate fall and containing innumerable "pockets" holding filthy water for months

He found that it was cheaper and less exhausting to inspect and arrange for the carrying out of necessary work than to worry the householder, issue a summons and then, in most cases, have to do the work and try to recover the cost in a court of law Merchants liked their agents and clerks to live close to, if not actually amongst, the natives who brought business and trade to the firm, and it was not thought right that white men should segregate themselves from their poorer brethren who were providing them not only with business but also with infection

The following year Ross was awarded the honour of Companion of the Order of the Bath, and elected Cameron Prizeman of Edinburgh University This year also he visited Ismailia, the headquarters of the Suez Canal Company, to investigate the reasons for the great increase of malaria there He and his party were housed in the President's palatial dwelling and he remarked "Aedes bit us all day, Culex in the evening, and a few *A pharoensis* occasionally" Ismailia itself was a town of only 7000 inhabitants, of whom 978 were French employees, accompanied by their families The town was scrupulously clean and the natives occupied a separate quarter which also was well kept

When the fresh-water canal had been formed in 1877 there were 300 cases of malaria, in 1900 there were 2284 cases and the prevalence and severity were such that a proposal was under discussion to abandon the town. Ross found numerous larvæ in a watercress bed, in several small irrigation pools and in a shallow fresh-water marsh formed by oozing from the fresh-water canal. There were fish in the canal itself and no larvæ were found there.

The domestic water-supply was piped from the canal, rainfall was small and canal water was used for irrigating the gardens. The canal and the permanent streams contained reeds and grass but were crowded with fish and no larvæ could be found. The subsoil water, however, was very near the surface and fluctuated with the rise and fall of the Nile. In hollows it formed lakes, ponds and shallow marshes. Careful search in the fresh-water canal and its branches and of the vegetation at their margins revealed no breeding-sites of *Anopheles*, nor were there any in the cisterns or cesspools of the houses, though *Culex* were numerous. *Anopheles* larvæ were, however, seen in large numbers in marshes connected with the natural waters round Ismailia, especially in the shallow collections, short grass and vegetation, where there were no fish. Such pools existed for miles around, wherever the subsoil water appeared above the surface in depressions in the ground-level. As the mosquitoes would not fly very far, Ross argued that the probable cause of the prevalent malaria was the small marshes lying in the midst of cultivation to the east of the town and a still smaller one close to the *abattour*. Drainage of these eastern marshes had been adopted and also filling in of others, but neither had been carried out adequately. The local authorities had not sufficiently recognized the fact that it was the small pools rather than the large that were dangerous breeding-places.

The puzzling question was: What was the source of the *Aedes* and the *Culex*? There were no rain-water tanks, cisterns or gutters incriminated because it was the dry season. There was good water-carriage drainage, but no sewers, sewage was discharged into pits beneath each house, and these pits were sealed except for a ventilation pipe prolonged up above the roof. A bucket let down through the manhole of the pit brought up a fluid swarming with larvæ. These on hatching out would escape up the ventilating shaft into the open air. A regulation that a tumblerful of oil should be added to each pit once a week cleared up the trouble. *Anopheles* were found also in the small fresh-water swamp near Suez and mosquitoes were found breeding in the hoof-holes in the mud. Records have been obtained of the

number of cases of malaria in Ismailia from 1880 to 1906 and they convey some interesting information. The figures in successive years were 400, 450, 480, 550, 900, 2000, 2300, 1800, 1400, 1450, 1900, 2390, 2050, 1750, 1100, 1350, 1150. These figures from 1880 to 1896 are probably not altogether accurate, they appear too much like 'round figures,' but from 1897 onwards they are probably more exact. 2089, 1545, 1545, 2284, 1990, 1551 (in this year Ross went out to Ismailia), 214, 90, 37, and in 1906 none.

Malaria along the Suez Canal naturally makes us think of Panama, which Ross visited in 1904. We shall have more to say later concerning the prevalence of disease in Panama, here we may note in passing Ross's remark.

It was pitiful to see the parks of rotting cranes and locomotives left by the French in consequence of the yellow fever and malaria, the latter being bred from innumerable stagnant pools and runnels between many crumbling hills, with an immense rainfall.

In 1906 he visited Greece and adduces the following to explain the prevalence of malaria there.

Greece in the time of the Persian Wars could not possibly have been in its present condition, while now malaria haunts almost every valley and the course of almost every stream, except in a few areas like the Attic Plain, leaving only the barren hills, where there is little water, safely habitable. I argued that the disease must have entered Greece about 500 B.C. by the introduction of *A. maculipennis*, or perhaps of infected soldiers or slaves from Asia, must have crept slowly up the valleys and destroyed their rural prosperity, as it did later in Mauritius, and so may have played a considerable part in the subsequent decadence of Greece.

Ross next visited Mauritius where, apart from the French population, there were some 260,000 Indians, and troops were stationed at Vacoas. We have said enough concerning the devastating outbreak of 1866, when a quarter of the St. Louis population are said to have perished and the disease spread round the coast and inland. Prosperity declined and in 1906, shortly prior to Ross's visit, the death rate was forty per thousand. There was a severe outbreak among a battalion of British troops which had lately arrived, five died and many had to be invalided. The spleen rate, says Ross, was 34.1 per cent.

Of Ross's visits to Cyprus (1913), Alexandria (1915), Salonika (1917-18), Ceylon (1926) and Malaya (1927), no detailed mention is needed. On 15th July, 1926, the Ross Institute and Hospital for Tropical Diseases at Putney Heath was opened by H.R.H. the Prince of Wales, and later a Central Industrial Anti-Malarial

Advisory Committee was constituted with Sir Malcolm Watson, who had done so much for malaria prevention in Malaya, at the head. The Institute was amalgamated with the London School of Hygiene and Tropical Medicine in 1934, on 29th June.

Many take up the attitude that since any heavy shower in the tropics will fill up pools, or form collections in the angles between the leaves and trunks of palm-trees, sufficient for *Anopheles* to breed, it is impossible to get rid of malaria mosquitoes and attempts at reduction are a mere waste of time and money. Ross's reply to this may be quoted as it expresses an opinion held by a majority of those who have studied the question intimately. It has been referred to already (see p. 175).

Only a proportion of the eggs of an *Anopheles* succeed in hatching out into larvæ at all, that only a proportion of these larvæ succeed in hatching out into adults, that only a proportion of these adults succeed in biting human beings, that only a proportion of these succeed in biting infected persons, that only a proportion of these succeed in biting persons containing ripe gametocytes, that only a proportion of these live long enough (say, one week) to mature the gametocytes in their bodies and to form protozoa, that only a proportion of these succeed in biting human beings again. The final result must be that only a very small proportion of *Anopheles* in a locality will ever succeed in infecting a new case.

Hence there is need, not to eliminate, but only to reduce below a certain figure. Each species of mosquito seems as a rule to like its own special kind of water collection for breeding—tubs, pots, broken bottles, gutters, drains, cisterns, wells, tree-holes, rain-water in palms and so on—but *Anopheles* prefers water on the ground—pools, puddles, ditches, hoof-holes, edges of ponds and rivers, marshes, pools on rocks, rice-fields, beds of rocky streams, drying water-courses, and sometimes wells and cisterns. Also adults may have their favourite feeding-places at night and resting places by day—outhouses, byres, old wells, pits, huts, native houses, eaves, cupboards, walls and ceilings in well-built bungalows and so forth. If they abound in or near a given house we may be sure they are breeding close by. As Hackett states

The important fact is not that there are unsolved and at present insoluble problems of malaria in the world. It is that there are thousands of communities oppressed for ages by the disease that could be liberated by a little thought, energy and money which would not be difficult nowadays to assemble and apply. The mechanism of malaria transmission is so delicate and complicated. Persistence is more important than perfection and whether control is a partial failure or a partial success depends on the point of view.

The cost of malaria is enormous, nay incalculable. As stated by Sir Malcolm Watson, it cripples thousands or millions of people for months or years, it often impairs the whole labour force of a plantation or of a village or town just when the crops require the closest attention, it fills the hospitals, which are expensive institutions, it often demands treatment- and maintenance-allowances, and it generally doubles (at least) the death-rate in localities in which it abounds.

It is often one of the most expensive items in the cost of military campaigns, and it has even caused the abandonment of whole villages and stations and of extensive areas of cultivation. We must always remember these facts when we talk of the cost of malaria prevention. Both malaria and malaria control cost money, but the former costs health and even life itself in addition.

It is cheaper properly to house officials, servants, coolies and labour forces than to stint on housing and pay out for treatment, invaliding and replacement. The expense of building proper coolie lines is far exceeded by the cost of annual outbreaks of malaria and loss of labour from sickness and the ensuing debility.

5 INVESTIGATION OF THE MOSQUITO-MALARIA THEORY

There has been not a little controversy regarding the question to whom is the credit due for suggesting and proving the mosquito-malaria theory of transmission? There are some who cannot hear that one iota of the glory should be taken from Manson, they maintain that the suggestion was Manson's, that Manson was constantly urging Ross and directing the work and that Ross was, as it were, the mechanical workman to put Manson's ideas into concrete form.

There are others who are equally insistent that, though Manson pointed out a possible line of research to Ross, it was the latter who then proceeded to formulate his own plan of action, to follow this in spite of many obstacles and little encouragement and to bring the work to a triumphant successful issue. They would seem to think that any credit given to Manson robs Ross of his due meed of praise and 'kudos'.

Of the third stage, what appears to us as a rather unseemly bickering between two big men—Ross and Grassi—we shall not say more than that the evidence goes to show that Ross was on the right track of proving the sequence of transmission in man, but from deficiency of human material demonstrated it in birds, and Grassi, following up Ross's methods, proved it with *Anopheles* and man and then went on to show the different species of parasite

for the different types of fever and so on This has already been sufficiently noted

At the cost of a little repetition, perhaps, we will again review the work as carried out by Ross, reported by him to Manson, and the attitude of Manson towards Ross's work

We have already shown that the idea of mosquitoes and marsh fevers being in some way connected was not of recent date, but had been adumbrated vaguely centuries ago Manson in 1879 had demonstrated the mosquito (*Culex*) transmission of filariasis Four years later A F A King, in America, propounded a mosquito-malaria doctrine, giving nineteen reasons therefor, on the lines of, or at least in harmony with, Manson's work of microfilaria transmission In 1892 H G Plimmer demonstrated Laveran's parasites to Manson People's minds were at that time still concentrating on the marsh air or water origin and did not seem to realize that the plasmodium, being a blood parasite, must escape somehow from the blood in order to keep up its life as a species Even after he had heard of the parasite Manson was unable to find it until Plimmer showed it to him Ross at this time had not seen it either, in fact he clearly did not believe in it even as late as 1893, for he was writing in the *Indian Medical Gazette* concerning 'the supposed hæmatozoon' The following year Manson demonstrated it to Ross and the latter determined to work out its life-history on his return to India from leave Eight years later Ross publicly announced in his Nobel Prize address at Stockholm how much he owed to Manson's counsel, advice and direction

In May 1895, Ross started on his quest, noting the transformation of crescents into flagellated bodies, he stated that 40 per cent of those sucked up by a mosquito thus flagellated, whereas only a small percentage was observed to do so in a sample of blood extracted from a finger He deduced from this that the stomach of the mosquito was the better, and usual, place for the transformation to occur In 1896 Manson, who had been elected a Fellow of the Royal College of Physicians of London the year before, delivered the Goulstonian Lectures, choosing for his subject the *Life-history of the Malaria Germ outside the Human Body* Bignami and Grassi were opposed to the idea that exflagellation played any part, at least any active part, in the life-history of the parasite and put forward the hypothesis that the flagellated bodies were produced by the dying struggles of the parasite This was soon disposed of by the following experiment The finger of a patient suffering from malaria was pricked through a small droplet

of vaseline, the whole—vaseline and blood—was scraped off with a cover-glass, pressed on a slide and examined. No exflagellation took place and in twenty-four hours the crescents were seen to be disintegrating and obviously dying without becoming exflagellated bodies.

In 1897, on 20th August and 21st, at Secunderabad, Ross discovered the 'bodies' or 'cells' in the stomachs of two 'spotted-winged' mosquitoes (² *A. stephensi*) which were among those which he had bred in the laboratory and permitted to feed on a patient whose blood contained crescents. The following month he saw the same things in another species of *Anopheles* (² *A. culicifacies*). The question was discussed with Manson and it was in all probability Ross's observation of the 'bodies' in the stomach of the mosquito, of their assuming a small worm-like shape (it will be remembered that Manson gave them the name of 'travelling vermicule') that gave Manson, who was essentially and primarily helminthologically minded, the more concrete idea of transmission of infection *via* the mosquito, though, it will also be remembered, he thought infection was brought about by drinking the water into which mosquitoes had fallen and died, or by migration of the dust of dried-up pools in which they had died. Ross writes concerning the process of exflagellation

Exflagellation was a profound induction of Manson to which I always give the highest praise, but it did not lead me very far. It gave me no clue as to the species of mosquito concerned. Only one genus of mosquitoes carries human malaria, only some species even of that genus do so, and only a proportion of individuals even when they belong to the right species, actually become infected by sucking infected blood.

A. rossii, for example, could not be infected by him, nor by C. W. Daniels later.

Manson concluded that the flagellar stage was an essential phase in the life-history of the parasite, even before MacCallum had explained their function, hence his constantly repeated advice and injunction to Ross, "Follow the Flagellum." He argued that exflagellation was a sign of life and since the flagella appeared only when the malarial blood had left the body their purpose must be the continuation of the life of the parasite in the world outside the human body. In 1897 confirmation of the hypothesis was obtained when MacCallum of Johns Hopkins University, watching the malaria parasite in drawn blood kept moist on a slide, saw flagella extruded and thrown off and enter, like spermatozoa into ova, other cells which had not exflagellated.

At home Manson was giving Ross all the backing he could. At the British Medical Association Meeting, held at Edinburgh in July 1898, Manson stated that Ross's observations

tend to the conclusion that the malaria parasite is really a parasite of insects, that it is only an accidental and occasional visitor to man, that not all mosquitoes are capable of subserving it, that particular species of malaria parasites demand particular species of mosquitoes, that in this circumstance we have at least a partial explanation of the apparent vagaries of the distribution of the varieties of malaria.

The first two sentences quoted above were indeed revolutionary, but nonetheless true. The mosquito, as being the body in which the sexual phase takes place, is really the definitive host, and man, in whom the asexual development occurs, is the intermediate host. It was just in time for the Edinburgh meeting that Manson received a telegram from Ross at Calcutta that he had found the 'pigmented cells' in the mosquito's stomach grow and produce 'spores' after about a week. Ross had been placed on special duty in January that year at Calcutta, to give him an opportunity of continuing his malaria researches, but finding few human cases in Calcutta he was forced to work with the malaria of birds.

The investigation which had been pursued more or less continuously for nearly four years was not all plain sailing. Ross again and again lost heart and as often resumed work at Manson's encouragement and instigation. All honour indeed to Manson for his far-sightedness and his tact in dealing with a man of Ross's temperament, but more than mere encouragement is needed for a man in the heat and discomfort of a tropical climate to work on in the face of set-backs and disappointments, obstacles and disheartening want of recognition among his superiors, however great may be the encouragement coming, he feels, from one who is living at ease in the cool and comfort of London. Let us review the course of events in a little more detail.

Between 1895, when Ross started his investigations, and 1899 when he left India, with a characteristic grumble because few came to see his work when he was in Calcutta and most of those who did regarded him as a visionary, he and Manson were in constant communication, he reporting progress and sending specimens, Manson studying them and giving his interpretations of them and encouraging and advising. He confirmed MacCallum's discovery. He used any mosquitoes he could collect—*Culex*, *Aedes* (*Stegomyia*) among them—with what we know now must have been very disappointing, but inevitable, results. Temporarily discouraged Ross reverted to Manson's not yet discarded

theory and tried to infect man by giving him water to drink in which mosquitoes had died after feeding on a patient suffering from malaria. Unmindful of Pasteur's dictum, "Be very careful when you are looking for a thing or you will be sure to find it," he thought he had succeeded and wrote to that effect to Manson. The latter in reply urged him to further efforts telling him to regard a set-back as a stimulus to try again, and advising him to examine the ova and larvæ of mosquitoes. In this Manson was probably thinking of the transmission of Red-water in cattle by ticks, established by Smith and Kilborne in 1893. He tried to impress upon Ross the value of his work, in a field broader than that of malaria alone, in one letter he writes

I believe a splendid work for a man to spend his life over would be the influence of the mosquito as a pathological agent

Towards the end of 1895 he suggested

Try to malarialize mosquitoes with ordinary tertian blood. Select the hot and sweating stage of the fever for feeding the mosquitoes. That is the time when the flagellate form abounds most in tertian blood [this, of course, is not so, the flagellate form occurs in the mosquito and not in the human body]. Is it not curious as well as suggestive that this is just the time when the mosquito has the best chance—the patient is prostrated and cannot defend himself—he has thrown off his clothes to cool himself and his skin is bathed with perspiration, damp and attractive

Just a year later Manson, clearly not having much faith in transmission by the bite of mosquitoes, wrote "It may be that the mosquito conveys the parasite in biting, but I do not think so—at all events I do not think it does so directly"¹

Manson was very jealous for British tropical medicine and the fame of British workers. To obtain support and encouragement for Ross from those in authority he wrote in a letter to Sir Charles Crosthwaite, in July 1897

In the matter of tropical diseases we should in virtue of our opportunities be *facile principes*. But even in tropical diseases Frenchmen, Italians, Germans, Americans, and even Japanese are shooting ahead of us. We have to get a Koch to find for us the cholera germ, and a Haffkine to protect us from it, a Laveran to teach us what malaria is, a Kitasato to show us the germ of plague and a Yersin or a Haffkine to cure its effects. This is very humiliating

¹ I do not understand the meaning of this last sentence, if he did not believe the mosquito to be a true host in the sense that a necessary stage of development took place in it, the only way it could convey infection would be by biting a heavily infected patient and almost at once transferring the contents of its proboscis into another subject, i.e. 'directly'. At all events, the preceding sentence proved in time to be erroneous—*Aliquando bonus dormitat Homerus*!

Ross soon regained confidence and turned with fresh zest to his problem and he was able to report that in the stomach wall of special mosquitoes, *Anopheles*, which had fed on a malarious patient, bodies which he had failed to find in his previous attempts, with *Culex* and *Aedes* (*Stegomyia*) Manson applied for the Indian Government to put Ross on special duty and, as already recorded, succeeded, Ross being sent to Calcutta for six months. Manson also contrived to interest the Colonial Secretary, Mr Joseph Chamberlain, and the President of the Royal Society, Lord Lister, in Ross's discoveries. The results of Ross's work at Calcutta need not be repeated, suffice it to say that during this time Manson's encouragement, stimulation and advice were never wanting. He sent specimens to Bignami in Italy so that the Italian malarialogists, who were striving hard for the same goal, should be made acquainted with what Ross had accomplished and thus be unable to 'jump his claim,' unwittingly or of set purpose. This was in 1898. How Manson arranged and carried out the double experimental proof of the theory to transform it into fact belong really to the life of Manson, but to make the matter complete brief reference may be made here. For the first part he allowed some *Anopheles* which had fed on a benign tertian malaria patient and had been sent to London, to bite two healthy individuals who had not been exposed to malaria, one of them his son, Thurburn. After the usual incubation period both suffered from malaria and the parasites were found in their blood. For the second, the converse of this, he and some friends, Sambon, Terzi and Low, the last of whom is still with us, went in 1900 to the Roman Campagna, near Ostia, a notoriously malarious place at the mouth of the Tiber, and put up a mosquito-proofed hut brought from England. They stayed within it from an hour before sunset to an hour after sunrise throughout the malaria season, July to mid-October, and remained in perfect health while the peasantry outside suffered severely. Thus Manson showed that infected mosquitoes would convey infection to the healthy in a non-malarious country, and *vice versa* that, with due precautions to exclude *Anopheles*, Europeans could live uninfected in a highly malarious district. This experiment is mentioned in the textbooks, but a similar experiment carried out in the same year by Mattei in Catania is less well known. He took four men, working in a malarious district infested with mosquitoes and prevailed upon them to remain in a 'proofed' house during the evening and night, but taking no quinine. During the thirty-three days of the experiment none of them contracted malaria.

6 CONTROL

We have now traced the subject of malaria down to the discovery of the causative protozoon and the mode of its transmission, the methods of control and, theoretically, its eradication are, therefore, readily deducible. We say 'theoretically' advisedly, because even though we know the way, the obstacles which nature puts in our path to success in carrying out the methods, in applying our knowledge, are in tropical countries at times insuperable. It is but natural for one who has not experienced the difficulties to say: You tell us you know the cause and can cure the patient, you know the vector and how she transmits infection, you know the life-history and the habits of the transmitter, you know how to prevent her biting, you know how to prevent her entry into our dwellings, you know how to prevent her breeding at all, you say you know all this and I believe you, why then, in the name of goodness, don't you get rid of it once and for all, lock, stock and barrel?

It certainly seems strange that with all our knowledge and after all our efforts malaria remains in some parts of the world as rife as ever, while in others, although no measures directed specifically to this end have been applied, malaria has disappeared.

This leads us to consideration of the question of control. All methods can be classed under one or other of three main heads: 1 Mosquito reduction 2 Mosquito exclusion 3 Cure of patients. Each method has its own place and is appropriate under certain conditions, in other circumstances two may be combined, sometimes all three will be necessary, as was exemplified by those responsible for the medical arrangements in the Panama Canal construction.

This book does not profess to be a treatise on malaria and a description of control methods adopted in various parts of the world is, therefore, not within our scope. In dealing, as we are, with the historical aspect the main features of the methods of control, on what they were based and how they came to be adopted, points such as these call for a few words illustrating the way in which, as time progressed and new facts became known, fresh measures of control were proposed and tried and those found serviceable retained, until we arrive at the methods in use to-day. The first of these questions has been sufficiently spoken of—on what grounds control methods have been based—the knowledge of the vector and the mode of transmission, its life-history from egg through larva and pupa to imago, knowledge of the parasite, its life-history. All these offer indications at some point or other

for breaking the chain of man-mosquito-man and it is the breaking of this chain which solves the question of prevention and control. The principles are clearly three. First, any potential insect vector should be prevented from becoming infected, that is, the mosquito must be protected from infection and this can, theoretically, be done by segregating the human source by means of a net screening and treating him until he no longer harbours the parasite. Second, protect the human subject from infection by a possibly infected vector, again, screening by nets from sunset to sunrise, or screening of houses. Third, extermination of the Anopheline vector. The former two are simple, the third not only very difficult, but often impossible to carry out. A considerable amount can be accomplished, thanks to the knowledge we have acquired as to the biology and ecology of the insect. By obliterating breeding-sites we prevent oviposition, at all events successful or fruitful oviposition, we can at a later stage take measures to exterminate larvæ, and later still tackle them in the adult stage. Mere enumeration of the various measures will suffice, bearing in mind that the same method of attack will not succeed with all genera of mosquitoes, nor with the different species of Anophelines. It must not be forgotten that some—*Culex* and *Aedes*—are more domestic mosquitoes, preferring to breed in small collections of water in or close to a house, whereas *Anopheles* breed usually in more permanent collections. The former would be dealt with satisfactorily by ordinary sanitary regulations, covering of cisterns, water-butts or other receptacles to prevent access of mosquitoes, not leaving water in any uncovered receptacle long enough for larvæ to develop, avoidance of surface drains, rectification of sagging gutters, dripping taps, care of soakpits and cesspools, removal of broken bottles and tins. *Anopheles* would call for larger and more extensive measures, such, for example, as filling up holes in tree-trunks, bamboo tops of fences, clearing of plants and undergrowth, supervision of aqueducts, wells, ponds, pools, runnels, edges of lakes, banks of rivers, swamps, fens, marshes, whether fresh, brackish or salt, seepage and small puddles in boggy land, crab-holes, rice-fields, irrigation channels, ditches, railway embankments, borrow pits. As we have said, the problem is rendered more difficult when, by clearing out a troublesome but not a malaria-carrying mosquito, we may make a way for the entry of a more dangerous species. We must remember also that species have their preferences, probably directed to satisfying physical, biological or chemical needs. This is closely connected with what has been said above,

its implication is that anti-mosquito measures should not be taken in hand unadvisedly, a preliminary survey is absolutely necessary with a view to determining the species present, whether that prevailing or some other habitually attacks man, which of them is actually carrying malaria. Only when this has been done can measures be adopted with any real hope of success, but after this we may pay attention to abolition of breeding-places as by draining, by repeated removal of vegetation, by clearing and cleansing channels, leading away the subsoil water. For this to be done on sound lines there is need for a study of the local topography, hydrography, geology and meteorology. At the same time there will be need of surface levelling, filling in of ponds and marshes, assisted in the latter by drainage, training and canalizing of meandering and stagnating streams, embankments for keeping out tidal waters, preventing silting up of water-courses, controlling irrigation channels, restricting cultivation which requires much moisture, attention to culverts and ditches—in short, a wide knowledge and application of sanitary engineering. Sometimes, in the tropics frequently, such counsels of perfection are impossible of fulfilment and we have to aim at destruction of larvæ, as by the use of oils, petroleum mostly, to form a film over the water by means of a sprayer or, for an extensive surface, a barrel with continuous drip elevated so far above the water-level that the fall will break up the oil-drop, for boggy ground sawdust soaked in petroleum has been found of value. The use of Paris green as a dusting powder in a strength of 1 per cent is now nearly universal and has proved of great value.

Two more recent developments, one for controlling breeding of mosquitoes in shallow water-courses, the other an antilarval measure, should not be omitted. The former is K. B. Williamson's 'Herbage cover' method, the latter Williamson and Scharff's suggestion of 'Antilarval sluicing'. The herbage cover method consists in covering the water with packed grass and herbage or with leaves and twigs mixed to form a brushwood drain. This is well trampled down until it forms a wall impenetrable to egg-laying mosquitoes. In stagnant or slowly moving water rotting takes place and *Anopheles* will not oviposit or breed there. This method when tried in *nullahs* in Orissa was most successful, *Anopheline* breeding being altogether eliminated. Probably much depends on the choice of scrub or vegetation used for packing, for in other places no rotting took place and breeding of mosquitoes was not affected. The method is, at any rate, inexpensive and is applicable for villages.

The essentials of 'Antilarval sluicing' are these Firstly, the rapid discharge of a sufficiently large volume of water, so best from that impounded in a reservoir above Secondly, rise of water in the sluiced channel, followed by a fall, so that eggs, larvæ and pupæ are stranded and become desiccated Thirdly, a change of speed in the sluicing current may destroy larvæ and pupæ by shock, by drowning, or by burial in silt Fourthly, reservoirs should be emptiable completely, so that they may not themselves become breeding pools, not reached by the sluicing Though pot-holes may form beneath the sluices, they are usually not more than a foot or two deep and the violence of the discharge prevents any larvæ surviving there In some places, Penang for example, permanent automatic syphons were installed so that the sluicing was itself automatic, this proved very successful and within a year the initial cost of construction had been repaid

In ponds or collections of water where there is not too much vegetation, the use of 'millions,' species of *Gambusia*, has proved a valuable larvicide in many parts of the world and early in the present century S G Dixon of America noted the activity of ducks as destroyers of mosquito larvæ in tanks and ponds

The placing of fish in drinking water to test its suitability is of old standing and arose, not with the purpose of destroying mosquito larvæ, but to convince the owner that his neighbour had not poisoned the water According to Morin and Martin (*Notions générales sur l'utilisation des poissons à la lutte contre les Moustiques*, Arch des Instituts Pasteur d'Indo-Chine) the use of fish as larvicides was first adopted by Gorgas in 1902 when attempting to rid Havana of mosquitoes Five years later Legendre adopted 'antimalaria fish-culture' in Madagascar

The question of clearing jungle with a view to eradicating breeding-haunts is one which calls for very careful preliminary investigation The dangers resulting from cutting down forest and thus removing what had been an effective protecting screen have already been referred to, as has also the added risk of getting rid of harmless species while opening the way for dangerous, malaria-carrying species Strickland and Malcolm Watson have clearly demonstrated this danger in Malaya Another instance which may be cited is Assam where cutting down of trees shading streams allowed the dangerous transmitter *A. minimus* to breed freely

We may interpose a remark here that though it is possible, even probable, that nearly all species of *Anopheles* can be infected under suitable conditions in the laboratory there are great differ-

ences in infectibility in nature and thus some species are much more concerned with the spread of malaria than are others. For example, Bentley collected in Bombay at the same time and from the same houses 837 specimens of *A stephensi* and 772 of *A rossi*. Of the former 10 per cent had oocysts in the intestine and 3.5 per cent had sporozoites in their salivary glands, whereas none of *A rossi* had either, showing that this mosquito was playing no part in the spread of malaria in Bombay. The inference from this is twofold. First, it stresses what has been stated already, namely, the need for noting which of several local mosquitoes is the real criminal in spreading infection, and, secondly, a knowledge of the habits of the *infective* mosquito before preventive measures are undertaken, for much money and time may be wasted in clearing away innocuous species whose expulsion may allow a harmful species to enter. This 'species sanitation' is not a problem of merely academic interest, it is of the utmost practical importance. The following, or comparison, points to several lessons which may be learned. Northern Java is highly malarious and *A ludlowi* and *A rossi* are both present in large numbers, but only the former of these acts as a carrier of malaria infection and is easily dealt with because, whereas *A rossi* breeds in all kinds of water, *A ludlowi* here breeds in salt water only. In Sumatra, however, *A ludlowi* breeds in fresh water, in the rice-fields, and is responsible for much of the infection there. Again, at the end of the Great War tobacco planters on the east coast of Sumatra had difficulty in feeding their coolie labourers and therefore planted rice for them. The rice-fields of Java and Borneo bred swarms of Anopheles, but the species was *A hyrcanus* which is not a carrier in those places. This species is abundant, but harmless as a vector, in the Yang-Tse and the Ebro, in Macassar and the Celebes, this fact was known and the Sumatra planters had consequently no fear of the rice-fields, with *A hyrcanus*, being unhealthy. Malaria, however, appeared and soon assumed epidemicity and examination showed many of these mosquitoes to be infected. The same species is also a common vector, even the principal vector, in other districts of Sumatra.

In South Africa *A gambiae* breeds well in small pools of water, free from weeds and exposed to the sun, in other parts of Africa it seems to prefer marsh or stagnant water with vegetation. In Holland there is a non-carrying fresh-water race and a carrying salt-water race of *A maculipennis* to be found. It is clear that we have advanced a long way from the association of ideas of mosquito abundance in general implying malaria prevalence. At

first sanitarians aimed at general reduction, or even abolition, of mosquitoes, this was found to be impossible and relief was felt when it was shown that, from the malaria point of view, *Anopheles* only had to be considered and dealt with now we have reduced the problem still further to 'species sanitation'—attacking those *Anopheles* only which are definitely implicated as the local hosts of the malaria parasites and transmitters of infection Nevertheless, in spite of all this and the narrowing of the issue, we seem to be making precious little progress in ridding the world of malaria

[A small digression will emphasize this point of species sanitation—the analogue of Filariasis in Little Hong Kong in 1936 Out of 11,169 dissections of *A. minimus* 153 were found infected, 1.4 per cent Of 424 *A. jeyporiensis candidiensis* 8 or 2 per cent, of 1104 *Culex fatigans* 16 or 1.4 per cent From this it follows that the second is the best host, but as the first is by far the most numerous it is locally the most dangerous In a neighbouring area the second still shows the higher percentage of infection, but here the number present heads the list by nearly a fourfold majority, 19,965 to 4818 of *A. minimus* caught and is consequently the greater menace]

A further point arises which may be touched upon here Darling has shown that a patient whose blood contains fewer than twelve gametocytes per cubic millimetre is not infective to mosquitoes, but a single mosquito which has fed upon a heavily infected carrier may be the cause of more malaria than many mosquitoes which have fed upon scantily infected carriers (Christophers), hence the actual number of carriers in a locality is of less importance than a much smaller number of heavily infected carriers

Lastly, we may make an attack on the adult mosquitoes They do not like sun and wind, hence it is well to get rid of their lurking places in and near dwellings by removing creepers, thickets and brushwood, by frequent inspection of cellars, outhouses, stables, and by covering wells They may be kept out by screening of doors, windows, verandahs and ventilating pipes (the danger of the last was amply demonstrated by Ross at Ismailia, see above, p 178), by using nets at night Mosquito traps are useful in some cases, those for *Anopheles* giving the best results when placed on the lee side of buildings, those for *Culicines* on the windward side

Many of these measures are modern developments based on old empiric means In 1876 a traveller in Siberia, named Pallas, found that the only way he could protect himself from the pest of biting mosquitoes was by placing a vessel of smouldering birch

bark on his back while walking Professor Whitfield reported nearly half a century ago that the people in Atlantic City, New Jersey, used to add copperas (green vitriol, or ferrous sulphate) to water collections to destroy mosquitoes, *i. e.* their larvæ

Sufficient has been said for the time being on mosquito reduction or exclusion Removing the human source of infection by treatment will be postponed for the present, but removal of the native source of infection for the European is easily done and is necessary in the tropics, by separating the native huts and the servants' quarters from those occupied by the white man The natives, especially the native children, are reservoirs of potential infection and if these live in proximity to the white man mosquitoes can readily transmit the disease from one to the other

So much for general principles of control In the tropics there are special difficulties to be overcome Thus, the *Anopheles* oviposit each month and in the wet season the breeding-places are rarely, if ever, dry, in Panama, for example, the flat and low-lying lands are breeding-grounds, or practically so, for eight months in the year, while in the dry seasons the largest streams and the small rivers are reduced and become alive with larvæ Writing on the Canal and Canal Zone in 1910 one author stated that the water in the bottom of the Canal in the dry season forms more than ten miles of continuous breeding ground Open ditches cannot be made serviceable for draining in the Zone because in a fortnight or so they become choked with algæ, and larvæ can exist where there are algæ, the latter afford protection so that larvivorous fish cannot get at them If removal of algæ is attempted the procedure would have to be done again in a week or so Again, in the tropics after a heavy rainfall, mere depressions in the ground hold sufficient water to allow of breeding, even though hidden by long grass Yet further, certain plants are constructed so that they retain water after a shower, for example the Bromeliaceæ or wild pine Boyce reports and pictures a single Saman tree which when cleaned yielded twenty-six cartloads or three and a half tons of epiphytes and each plant could hold $\frac{1}{2}$ –1 pint of water This single tree was thus as serviceable for breeding *Anopheles* as a fair-sized pond

P F Russell, writing from the Philippines on the *Epidemiology of Malaria*, says

The longer one observes malaria in the tropics the more one is forced to conclude that, so far as average rural areas are concerned, the problem of control is still unsolved Malaria prevention in the tropics by means of drains and subsoil pipes, larvicidal oil and Paris

green is entirely feasible in cities, organized industrial and agricultural centres but for most malarious rural areas in the tropics it appears that we have no economically feasible control measures. So far as I know, the drugs, quinine, plasmoquine and atabrin have never eradicated malaria from an area or even from a single town.

Drug prophylaxis will be mentioned later. The above is a depressing summary, but we are bound to admit that it gives fairly accurately the position to-day—a state very disappointing when we thought nearly forty years ago that the solution of the problem was in our hands.

Nevertheless, even in the face of this, it would be the height of folly to throw up the sponge and permit the rule of *laissezaller* to hold the field. We must continue to wage war and the following must continue to be our lines of action, after our preliminary survey.

- 1 Vital statistics must be kept of the labour force employed, giving us constant and comparable evidence of the age, sex, sickness, mortality and invaliding rates and the causes of sickness, invaliding and death, at regular intervals.

- 2 Coolie labour must be selected and chronic malaria carriers be weeded out.

- 3 Medical inspection of the labour force, their quarters and lines must be careful, thorough and frequent, also examination of the blood of all fever cases and suspects.

- 4 The sick must be thoroughly treated and not allowed to mix freely with others as soon as acute symptoms subside.

- 5 Last, but certainly not least, come the social and economic measures—the character of the food, the wages adequate to purchase proper food, good water-supply, properly supervised, housing, personal hygiene, latrine provision and general sanitation, filling in of borrow pits which too often have been allowed to become the labourers' bathing place, latrine and even the source of their drinking water.

It would hardly be necessary to stress further these social and economic factors had they not been so much neglected in the past and hence come to have an historical interest on the subject of prevention and control. It is so clear at the present day that any circumstances tending to delay recovery or to lessen the patients' resisting power, to increase exposure to infection or foster close association between a malaria carrier and susceptible potential recipients must enhance both prevalence and severity. Mere enumeration of some of these factors will suffice to show their menace. Aggregation of labour in tropical undertakings, such as jungle-clearing and engineering works (see Panama Canal, later), coolies employed are mostly from the poorer classes, have often come a long distance to find work, live on poor and often

unaccustomed food, under their new circumstances, are housed, often crowded, in huts of temporary construction, are doing arduous work under varying climatic conditions with clothes unchanged, pay small, and food and clothing insufficient, and surroundings insanitary

We will now give a brief account of two or three instances in which the application of these control measures has met with real success. Perhaps the most striking of all is the success of the Americans at Panama and Colon, which enabled them to build the Panama Canal after Lesseps' catastrophic failure in 1881-6. This, however, necessitated dealing not only with malaria but yellow fever and other diseases also, and is too important to speak of incidentally merely. It demands a chapter to itself (see later). We will content ourselves with reference to Les Dombes, the Roman Campagna and Malaya.

The carrying out of methods of prevention and control of malaria on a large scale, necessitating extensive engineering and construction work, drainage and such-like, is spoken of under the name bonification. Les Dombes in the Rhine basin was a rich alluvial plain liable to periodic flooding. These floods filled a system of specially constructed pools and in connection therewith there had grown up in the course of time special rights of pasture, retting flax and others. Almost the whole area was in the hands of the clergy and the *noblesse*, these let the land out to poor farmers who were badly housed and even by hard continuous work could make little more than enough to pay their rents. The peasantry were ill-housed, ill-clothed, ill-fed, and many of them lay down at night with their cattle. As long ago as 1790, at the time of the French Revolution, the inhabitants begged that steps might be taken to abolish these pestilential ponds and flooded areas, they reported that deaths exceeded births and no one lived to the age of 60 years. During the nineteenth century the question of drainage was taken up but was hotly opposed because it would interfere with the fishing and fish were plentiful. By 1870 the pond areas had been reduced by three-fifths, from 20,000 hectares to 8000 and a railway from Bourg to Lyons passed through the district. In 1837 and again twenty years later malaria was very severe and continued so till 1863 and after. For a long time, in fact down to the present day, even though the flooded area had been so much reduced *Anopheles* larvæ abound in many of the ponds and the adults are said to be present 'in millions' in byres, stables, piggeries and poultry-sheds. Although the mosquitoes were still numerous in the residual ponds between 1880 and 1890

malaria fever disappeared. More cattle were kept, the farming improved, the railway led to the opening up of more markets—in short the condition of the peasants was vastly bettered. The importance of agriculture, and especially the keeping of cattle, in bonification and prevention of human malaria will be referred to again.

Let us now turn to the Roman Campagna, the bonification of which has been one of the triumphs of modern anti-malaria measures. We have already spoken of the prevalence of malaria there and now will say a few words as to the manner in which it was dealt with, since it has some historical interest. Anna Celli-Frantzel, writing of the Roman Campagna and the district, says that the French, by establishing the monks of Cluny there at the end of the tenth century, the Cistercians in the middle of the twelfth, and the Trappists in the nineteenth centuries, have not ceased to send a succession of colonists to spend their energies in the pestilential territories of Rome. Of these earlier days we will not speak but come to the last century. At the beginning of the nineteenth century schemes were brought forward, not this time based on zeal for religion but on engineering enterprise. In 1810 Napoleon had expressed anxiety that the causes of the decadence of the Roman Campagna might be investigated and a desire for their remedy. In 1824 and 1856 Claude Bayon, Linotte and Froyer carried out works at Ostia, and in 1828 Littard proposed a scheme for draining the Campagna, the cost, however, was prohibitive. A report in 1831 speaks of the undertaking as follows. In Rome a lake near the Villa Borghese was to be drained, stagnant waters around the Forum were to be led away by reopening the Cloaca maxima and a series of quays were to be constructed along the Tiber for protection against flooding. Half a million francs were given for planting tobacco, indigo, cotton and rice in the environs of the city. In the Campagna orders were issued for the planting of trees along the roads, cultivation was extended and merino sheep were introduced. A great work of canalizing the Pontine Marshes was begun and about one-fourth of their area was recovered for cultivation. In addition a project was brought forward for draining the Maccarese. These projects had to be abandoned on the score of expense.

In 1900 Grassi carried out some experiments on the inhabitants to prove that malaria was due to infection by the bite of *Anopheles* and not to inhalation of the air of infected districts, and, secondly, to protect them from the bites of mosquitoes by the use of wire blinds to doors and windows. At the same time Professor Fermi

and Dr Lumbao experimented with repellents, such as animal fats, essential oils, animal extracts—of reptiles, amphibia and fishes—“ which are not attacked by mosquitoes ” Tests of these were made on the inhabitants of the Pontine Marshes and of Sardinia, but they were found to be ineffectual after an hour or so

For the next twenty years little if anything was done Then in 1918 a survey of the marshes was undertaken by the officials of the Office of Works This took some years and it was not until 1924 that a real start was made By 1933 the natural water-courses had been regulated and nearly all the floods and stagnant pools eliminated Owners of the land, deterred by knowledge of former attempts, were averse to sinking capital in erection of new buildings and in the introduction of new farming methods, so the Duce called on the National Ex-servicemen's Association to carry out his programme of land-improvement for agricultural ends In 1931 18,000 hectares of land were given to this association By that time the upper waters had been canalized and collected into the great Mussolini drainage canal and led to the sea The land was divided into holdings, more than 500 farm-houses were built and instruction in rational methods of farming was given to the peasants Doors and windows were screened and the soil prepared and stocked before the land was handed over In the early days of this vast undertaking the workmen were brought to the site daily in motor-coaches, later, huts or barracks were constructed for groups of 500 to 2000 workmen whose health was properly looked after The land having been got ready and stocked was handed to the peasants and a town grew up In December 1932 the Commune of Littoria was officially constituted and “ what twenty-five centuries had attempted in vain was accomplished ” By October 1933 nearly a thousand new houses were to be ready for occupation and six months later the new Commune of Sabandia was to be inaugurated and in a further six months a third Commune, that of Pontina The rapid growth of the population in the Agro Pontino is shown by the following figures In July 1924 they number 1800, in July 1932, 12,000 and by July 1933, 40,430 Health services were placed under the Red Cross administration Prophylactic quinine was employed but almost limited to those not permanently resident Arrangements were made for early diagnosis of cases and prompt treatment and persons found carrying infection were followed up and adequately treated The houses were inspected for the presence of adult *Anopheles* and when found these were destroyed by fumigation, anti-mosquito squads carried out the usual methods of

eradication by oiling and the use of Paris green according to circumstances Zoophily (see below) was taken advantage of and the number of cattle increased in some districts to deviate the mosquitoes from human subjects In August 1933 a seaside colony was inaugurated at Torre Olevola for children of the settlers Torre Olevola, which is three kilometres from Terracina, was formerly a stagnant marsh with gigantic water-lilies and a haunt of malaria, bonification has succeeded well there also, and no cases of infection occurred among the children sent there

In 1933, though the number at risk was more than three times that of 1932, the morbidity rate fell to 2.09 per cent and the death-rate to 0.34 per mille—a wonderful achievement

The change may be summed up in a few words In the Roman Campagna prior to bonification the population was scanty and highly malarious, the people showed yellowish complexions, eyes dull, the children were sluggish and had large spleens, agriculture was in a primitive state and the land impoverished After bonification the population increased, the men became vigorous, the women rosy-cheeked, the children active, large barns and factories were erected and the land yielded copious crops of lucerne

Similar success has resulted from schemes to improve the sanitation, or rather bonification, of the plain of Salerno Pæstum, Battipaglia, in fact this district generally had till then been highly malarious As a result of the precautions taken, which need not be again detailed, the local peasants have been free from infection and newcomers have not contracted malaria

Lastly, Malaya Sir Malcolm Watson has described the early state and the improvement effected in Malaya in his *Twenty-five Years of Malaria Control*, from which the following is extracted

When first announced in 1898 Ross's discovery was treated with undisguised incredulity, when confirmed it was said to be interesting but valueless The honour of being the first in the Empire, and perhaps in the world, to use it successfully belongs to the Government of the Federated Malay States Malaria control by drainage was begun early in 1901 and before long the towns of Klang and Port Swettenham were completely freed from the disease Then came the larger problem of rural malaria In 1905 the Federated Malay States Government gave 110,000 dollars to drain the Kapar district Again success came quickly

But in the Malayan Hills with swiftly running streams there was failure Ten years after Ross's discovery the situation was grave, attempts at control had been abandoned in West Africa in 1901, says Watson, the idea had been unreservedly disowned with condemnation of mosquito control in India in 1909 In

1911 subsoil drainage and the putting of streams underground were started in Malaya and Singapore. In 1914 it was discovered in the former that kerosene and crude oil mixed would destroy larvæ in running streams. In that year also Strickland showed that in Malaya *A. umbrosus*, the pest of shaded water on the plains, did not breed in the hills, nor, so long as shade was maintained, did any other species of *Anopheles*, "a demonstration of the biological method of control." In 1916 the International Health Committee of the Rockefeller Foundation built a research laboratory at Klang and in charge of it was Malcolm Watson, here species control—destroying or abolishing only the species considered dangerous and ignoring others—was carried out. The method has been applied elsewhere. In Georgia, for example, "after nine years' careful work the Rockefeller Foundation is employing the methods which have commended themselves to workers in Malaya for many years" (this was written in 1928).

As regards Port Swettenham, Watson, knowing the conditions of the place and its environs, warned the Government of the Malay States five months before the port was opened that "the Government staff shortly to be stationed there will be seriously affected." The predicted outbreak duly took place and was so severe that the High Commissioner telegraphed from Singapore an order for the port to be closed. Through Watson's intervention the order was suspended until an anti-malaria scheme which had been recommended had been carried out. This was done and the port was saved.

Here is a convenient place to stress once more the importance of considering each place and the measures most suitable for dealing with the problem there—in other words, not applying haphazard a method which happens to have succeeded elsewhere under, it may be, quite different circumstances. For example, in some places—parts of Italy may be cited—malaria may be suppressed by excluding salt water from breeding-places. In others, an epidemic may be suppressed by letting salt water into the breeding-places. As an instance we may refer to Falmouth in Jamaica. Here there was a salt-water swamp, this was washed by heavy rains, the culvert between it and the sea became blocked, fresh water filled the swamp, algæ grew, *Anopheles* bred there in abundance and an epidemic of malaria occurred. On the outflow being unblocked and sea water being again admitted the breeding ceased and the plague was stayed. Similarly, in Trinidad in the swamps to which sea water has been admitted and has free play in and out daily, owing to defective sluice gates, no mosquito

breeding occurs. Consequently, the recommendation has been made that culverts should be installed whereby the swamps would be drained at low tide and the sea water admitted at high tide, thus a salinity of some 80 per cent sea water could be maintained and breeding prevented.

In Trinidad irrigation of the rice-fields was accomplished by obstructing rivers and main drainage channels, as a result there was produced as good an example as anyone could wish for demonstrating man-made malaria.

Yet another instance is the invasion of Lower Bengal by *A. sundarcus* in 1930. The presence of this mosquito had long been known in the Sunderbans and it occasioned a severe outbreak of malaria at Budge Budge, on the Hooghly, sixteen miles below Calcutta in 1930. The number of breeding-places within the Calcutta Corporation limits was only three in March 1934, a year later they numbered thirty-six. In the autumn of 1936 they caused a severe outbreak in Eastern Calcutta. *A. sundarcus* is a good traveller, it often goes by train but prefers boats, and it is by the latter that its range has chiefly been extended. Bunds were formed for fish culture and land was reclaimed for rice culture, these, together with Calcutta's sewage outfall, caused silting up of the Bidyadhari River and made a large part of the area suitable for *A. sundarcus*. In addition an extensive clearance of mangrove was made in Sunderbans. Also to be noted is the fact that in its advance this mosquito has shown an increasing adaptability to breeding places of lower and lower salinity.

Mention has been made of zoophily, or the preference of some species of *Anopheles* for the blood of animals to that of man. This is of historic and no mere academic importance in malaria, malaria prevention and reduction. E. Roubaud was the first to point this out and its influence as regards malaria and agriculture—the rôle of domestic animals, especially cattle, in malaria prophylaxis. He maintains that it is not reduction of *Anopheles* which renders countries non-malarial, but that freedom depends essentially on the preference of certain *Anopheles* for animals rather than man—*zoophilism* as opposed to *anthropophilism*. Man will under these circumstances be attacked if there are too many *Anopheles* to obtain satisfactory feeds on the available cattle, or if the cattle are not properly placed to offer them the choice, or if the cattle or stock be of the wrong kind. If the first prevails antimosquito measures are called for. If the second, measures will depend on whether the prevailing vector is a house-feeder.

or not, if it is, the animal houses should be arranged so as to interrupt the route between the breeding grounds and the dwelling, whereas, if it is not, the animals should be grouped in the open. Thirdly, the cattle may be of the wrong kind to attract the mosquito in question. Cattle (cows in byres) are a good scapegoat for man liable to be assailed by *A. maculipennis*, buffalo for *A. ludlowi*. This observation of Roubaud is supported by F. W. Cragg who found that when in years of plenty cattle were many in an Indian village malaria would be little, whereas outbreaks would occur after rainfall succeeding famine years with heavy loss of cattle.

Roubaud has thus stated in more scientific language facts which had been observed and recorded a century before by Denham, Clapperton and Oudney (*Narrative of Travels and Discoveries in Northern and Central Africa in the Years 1822, 1823 and 1824* London: John Murray, 1826). Dr Oudney states

Here would be my quarters for the night. They assured me that the mosquitoes were both so numerous and so large that I should find it impossible to remain, and that the horses would be miserable. They advised our retiring with the cattle to a short distance from the water, and sleeping near them, by which means the attention of these insects would be taken off by the quadrupeds. Englishman-like I was obstinate, and very soon falling asleep, although daylight, I was so bitten by mosquitoes that I was glad, on awaking, to take the advice of my more experienced guides. We determined on seeking the cattle herd and taking up our quarters for the night with them and although, previous to leaving the lake, my face, hands and back of the neck resembled those of a child with small-pox, from the insects, yet here I slept most comfortably, without being annoyed by a single mosquito.

L. W. Hackett, with A. Missiroli, has done much towards elucidating this problem. They noted, as have many observers, that malaria disappeared in certain regions without any direct efforts aimed at their elimination and even in spite of the continued prevalence of *Anopheles* in numbers greater than in other places which had remained highly malarious. They noted that this occurred often in well-defined zones in the heart of malarious regions, e.g. Valdichiana and Massarosa in Tuscany. It was not due to *Anopheline* immunity because the local species, *A. maculipennis* brought from Massarosa could be infected with ease in the laboratory. Nor was it due to elimination of gametocytes through effective treatment or to enhanced natural resistance in a prospering community. Gametocytes in a malarious population, they say, are never so reduced that transmission cannot occur if there are enough *Anophelines*. [This is shown by the fact that severe

outbreaks may follow unusual invasion by mosquitoes of an area which has been practically free for years. Thus, the Nemi Province of Rome had never been malarious within knowledge, the number of Anophelines were too few to insure transmission. When the lake level was lowered to reveal the sunken barges of Caligula, mosquitoes bred freely in the exposed flats and a severe outbreak of malaria ensued.]

The presence of Anopheles in numbers with absence of malaria is ascribable to lack of contact between man and mosquito and the importance of zoophilism is demonstrated by the following. As in many districts where malaria occurs among the poorer peasantry, the people live in a room over the stable. On a certain day a collection was made of Anophelines in the stable and in the living-room above it. In the former 1626 were captured, of which 98 per cent were females, and in the latter only 57 altogether, 51 of them females (89 per cent), of these last only three had fed on human beings while 1300 had fed on cows or 1400. This relation is termed the 'stabular attraction' of a locality. In farms in intensely malarious parts of the Pontine Marshes in 1931 the proportion of human to animal feeders was 1 to 8, although the bedrooms were large and lofty and the stables were dark and humid.

Hong Kong affords a good example illustrating the advantages of zoophily or animal deviation. At Shing Mun where there are no cattle nor—strange this in China—no pigs, there are four species of Anopheles found, namely *A. jeyporiensis*, *A. minimus*, *A. hyrcanus* and *A. maculatus*, and examination of large numbers of these showed that 89 per cent of them were engorged with human blood. At Wo-Li-Hop there are many oxen, buffaloes and pigs, and the cow-house, though at times a separate building, is often divided from the dwelling merely by a wall. Of ninety-two specimens of Anopheles caught there only seven had fed on man. Twenty-six *A. minimus*, the worst of the local transmitters of malaria, were examined, and all but three had fed on buffaloes. These tests were made recently, in 1934.

Again, in Shanghai, 300 specimens of *A. hyrcanus*, a frequent vector there, were examined, 295 had fed on buffaloes, four more contained both buffalo and human blood. Of another thirty-five examined all were, without exception, positive for buffalo. *A. hyrcanus* is readily infected experimentally by human blood and the inference is that zoophily seems to play quite an important part in safeguarding man against malarial infection in Shanghai.

The reasons for a mosquito being zoophilous or anthropophilous are not known. Experiments carried out with a view to deter-

mining the cause are not conclusive, whether it is a matter of scent or of food preferences. The following experiments have some historical interest. Cows were moved to a white tent and men entered it later, *Anopheles* swarmed in it, when clean straw was laid down the mosquitoes coming in were few. The opposite of this was tried, cow-dung was placed in the men's sleeping-room, mosquitoes were attracted and entered but did not bite the men sleeping there.

In another experiment *A. atroparvus* were let into a cage midway between a man in one box and a pig in another. The cage communicated by a length of stove-pipe with each box and the mosquitoes had the whole evening and night in which to make their choice. The pig proved on the whole to be the more attractive, but the choice seemed to depend primarily on temperature and, to a less degree, on humidity of the air. If the temperature was insufficient, increase of humidity could reinforce it. *A. labranchiae* is generally believed to have a preference for human blood, but experiments on lines similar to the above did not confirm this.

An hypothesis has been adduced that *Anopheles* born with a preference for animal blood multiply to such an extent that they oust those preferring human blood. This is pure hypothesis, but it may be noted that Raffaele bred in his laboratory eight generations of two strains of *Culex pipiens*, one eagerly attacked canaries, the other starved even though the birds were present. Other strains occur in nature which will feed only on reptiles and not touch birds or man.

We may say that it is highly probable that mosquitoes need stimuli in order to find food, and when they enter, say a pigsty in the morning, it may not be primarily to find a host, but for shelter. The temperature and humidity of the air coming from houses and sheds at the time of greatest activity are above that of the air outside and together these attract the mosquito, e.g. *A. atroparvus*. Similarly, in small working-class dwellings, often overcrowded, the heat and moisture in malarious districts are tempting to the mosquito and the 'malariousness' of such houses is ascribed partly to the numbers of mosquitoes found in them and partly also to the facility with which even a few infected mosquitoes could bite a relatively large number of human beings.

A good deal has been said regarding the place of larva-destruction in malaria control. For the sake of completeness a few words on the historical aspect of the use of larvicides are called for. Apart from vague remarks on the use of oil we have been unable

to find anything pointing to its use for actual reduction of mosquitoes prior to 1793 when, in connection with a yellow fever outbreak in Philadelphia, the American *Daily Advertiser* of 29th August, 1793, published the following

As the late rains will produce a great increase of mosquitoes in the city, distressing to the sick and troublesome to those who are well, I imagine it will be agreeable to the citizens to know that the increase of those poisonous insects may be much diminished by a very simple and cheap mode, which accident discovered. Whoever will take the trouble to examine their rain-water tubs will find millions of the mosquitoes fishing about the water with great agility, in a state not quite prepared to emerge and fly off. Take up a wineglass full of the water and it will exhibit them very distinctly. Into this glass pour half a teaspoonful, or less, of any common oil which will quickly diffuse over the surface and by excluding the air will destroy the whole brood. Some will survive two or three days, but most of them sink to the bottom, or adhere to the oil on the surface within twenty-four hours. A gill of oil poured into a common rainwater cask will be sufficient. A large cistern may require more, and where the water is drawn out by a pump or by a cock, the oil will remain undisturbed and last for a considerable time.

It is generally believed now that the action is not lethal by exclusion of air alone, but that the oil has also some toxic action.

As regards larvicides in powder or solid form Roubaud in 1920 reported that powdered trioxymethylene sprinkled evenly on the surface of water causes destruction of *Anopheles* larvæ through their swallowing it. He suggested that ponds or other collections of water might be treated with it at regular intervals to prevent development of adult *Anophelines*, since the powder in no way rendered the water unfit for use or poisonous to cattle or fish. M. A. Barber and T. B. Hayne the following year confirmed this. In their endeavours to find some cheaper and more poisonous substance (which, therefore, might be used in smaller amount) they observed that compounds containing arsenic gave very good results, and of these the most effective was Schweinfurt green or Paris green, a double salt of copper acetate and copper meta-arsenite, with the formula $\text{Cu}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 3\text{Cu}(\text{AsO}_2)_2$. This was no new preparation, it had been a commercial product for nearly a century, prior to 1870 as a pigment, after that as an insecticide for the Colorado potato-beetle. In 1926 Avery prepared a series, substituting formic, propionic, butyric, monochlor- and trichlor-acetic acids for the acetic acid and he showed that Paris green and its homologues are definite compounds of copper meta-arsenite and the copper salt of the acid, the ratio of the two constituents being practically 3 : 1 in all. More recently Hexa-

chlorethane, C_2Cl_6 , has been recommended as a larvicide. A thin layer of this powder spread on the surface of water kills larvæ and pupæ of all varieties of mosquito and does not make the water unfit for domestic use or for watering vegetables. It does not harm fish, crustaceans, or water-plants and is not toxic for man or animals, it penetrates readily amongst algæ and water-plants and is inexpensive.

Of late years the dusting has been carried out by aeroplanes, travelling at a speed of sixty miles an hour and at a height of 125–200 feet according to the velocity of the breeze, the amount used is about one pound per acre, and a dilution of 1 : 3 (for hand-spreading 1 per cent with road dust was used). Tests carried out in this way showed that penetration of the local vegetation was good and larvicidal power great and one plane could deal with an area of twenty square miles in a day.

Having traced the discoveries regarding the cause, the mode of propagation of malaria and the control measures based thereon, let us review the position in recent times and see how far those measures which are rational and based on real knowledge and on real scientific lines have accomplished what they were expected to do—abolish malaria. No impartial observer can affirm that the results are other than disappointing.

When the Malaria Commission was created in 1923 the general idea prevailed that all that was required was for malarialogists from various countries to join hands, pool their knowledge and arrive at some general plan of action to deal successfully with the problem. The conclusion has been proved wrong, partly because knowledge of the epidemiology of malaria is not so complete as we thought—there are many gaps to fill—partly because, though the remedy may be known, conditions make it impossible to apply them. Many thought on these lines. There are countries—England and the Continent, for example—where malaria used to be rampant, but where it has now dwindled to insignificance or whence it has disappeared altogether. If we can only find out, and this ought not to be very difficult, by what means this change has been brought about, then we can apply the same in countries less fortunate. Then came a difficulty, for investigation showed that in some countries whence malaria had disappeared no specific reason could be found. This very ignorance stimulated research and the discovery was made that, in benign tertian malaria, there may be long latency and that strains of parasite may exhibit changes of vitality.

Again, the idea was very general that drying up an acre or so of marsh, cutting a drainage ditch, and spraying oil on collections of water were satisfactory antilarval measures, but things are not so simple as this. Measures have to be based on direct experimental and field investigations before any plan likely to succeed is prepared. 'Prevention is better than cure' is an adage applicable to disease in general, but in the case of malaria prevention without cure is futile, if by this we mean control measures alone, neglecting the treatment of carriers.

Others take a more pessimistic attitude still, they say that in spite of half a century of discovery and research we seem to be making little, in many places no, headway in eradicating malaria. Millions still suffer from it every year and hundreds of thousands die of it. It is said that in India alone more than a hundred million persons affected in a year with malaria never see a doctor or take a dose of quinine or any other drug. They acknowledge that though drainage has done much, though screening is good, quinine is not an infallible cure and that with all our control methods there seems to be an unsurpassable limit. Deaths from malaria must reach an enormous total every year, James in 1920 estimated that in an average year there were 1,300,000 deaths from endemic malaria in India alone. Prevention by bonification methods may not be very difficult of attainment in dry tropics, but in the wet a single heavy rain may undo weeks of effort, for the palms will retain sufficient water for *Anopheles* to breed, thus, though the cause is known and the methods of prevention theoretically well understood, the end may be impossible of attainment.

There is another side to the question, where the known measures might bring relief, perhaps remedy, 'sloth and heathen folly' may nullify all our efforts. Thus, in Shanghai to dry up breeding-sites, to convert stagnant pools into running streams, to poison larvæ with Paris green or asphyxiate them with oil, or introduce larvivorous fish were, none of them, impossible, but the inhabitants objected to interference, oil was 'too smelly' [it is strange to think of anything being regarded as 'too smelly' in a Chinese town], Paris green killed the ducks, fish were a delicacy for the Chinese and the ducks, and, to crown it all, fear of political consequences slowed down the zeal of the municipal authorities, and the incidence of malaria among the British troops rose from 26.9 per thousand in 1929 to 77.2 in the following year (*Health of the Army*, 1930).

This, however, is not the whole question. On the other side

it is to be remembered that few large towns have as much standing water as Shanghai, and the majority of the ponds are used, not only for washing clothes, but also for washing rice—clearly a dangerous practice—and this is given as the reason for not employing Paris green as a larvicide

A. hyrcanus var *sinensis*, the vector of malaria in Shanghai, breeds in grassy furrows left in abandoned previously cultivated land, in shady pools and creeks. The increased prevalence of the disease in Shanghai in recent years is attributed also to road-making in low-lying land. The larvicide which has been found most effective here is the pyrethrum-soap-kerosene mixture of Ginsburg. Fish (*Gambusia*) has been tried, but the results have not been satisfactory.

It is important not merely to note but constantly to bear in mind that the discovery of appropriate methods of control does not necessarily imply their adoption, that progress in research does not ensure correspondence in application. Even with the knowledge we have acquired and with all the goodwill in the world progress may be hindered and retarded by lack of scientific direction or of labour to apply it. There is a twofold need “unitary and skilled specialist direction co-ordinating effort, and the labour to make it good,” as Professor K. B. Williamson has succinctly expressed it, “specialist direction upheld by Governmental sympathy and implemented at need by administrative action is the first necessity.” The people must be prevailed upon to help themselves if malaria is to be abolished.

Under war conditions difficulties are naturally much greater. C. M. Wenyon has recorded his experiences in this connection in Macedonia during the Great War. In 1916 there were over 30,000 cases and in the following year still more because submarine activities prevented removal of the men infected, in 1918 their prompt removal led to better results. Ordinary anti-mosquito measures failed, being impracticable under war conditions, prophylactic use of quinine was disappointing, probably owing to the frequency and intensity of infection. In 1919 when the Army moved into Turkey groups of men who were not taking quinine all became infected very soon. Work on the vectors showed that some of them hibernate and that larvæ can live even after being frozen and develop when spring arrives, while the adult forms live secluded in houses and cattle-sheds, and some may show partial development of parasites and this may be completed in the succeeding spring.

Again, in East Africa, though this was but a subsidiary theatre

of the War, 300,000 allied troops were employed and the morbidity rate, mostly from malaria, was very high, probably higher than in any other, the total admissions on this account being estimated at 250,000. Palestine, after the War, is an example of ill-considered occupation. When its colonization was undertaken the promoters of the scheme acquired swampy but fertile tracts and set about their occupation without any preparation (the reverse of the bonification plans in the Agro Romano already spoken of), the results were naturally disastrous and the malaria incidence intense. When once proper control measures had been introduced and were in working order the disaster was transformed into a successful venture.

7 PREVALENCE IN RECENT YEARS

Malaria still exists in England and the following places were still suspect some time after the War: the Isles of Sheppey and Grain, Sandwich, Romney Marsh, Borden and Longmoor in the Aldershot area. As late as 1925 alarmists were predicting an epidemic of malaria unless *Anopheles* were at once exterminated, but, as Alcock pointed out, *Anopheles* and malaria are as native to England as are sparrows, and he recalled that "the bill of mortality for the London area for 1665 included 5257 deaths from fever and ague." It is to improvement in sanitary environment, with no thought of mosquito or plasmodium, that disappearance of malaria from England must be attributed, "since fifty larvæ may even now be caught with one dip of a cup in July and innumerable adults in a stable in October within a few hours of London." Improvement is ascribable to drainage and better housing.

There is no general concord of evidence [writes Alcock] that the insect prefers the blood of cattle to that of horses, or pigs, or rabbits, or man, though there would perhaps be more general agreement that it prefers a cattle shed or a stable, even when empty, to a well-constructed house, even when it is inhabited.

The same is true probably of Holland of which Thyssen in 1824 wrote "If we exclude Italy, there is perhaps not a country where intermittent fevers are so malignant." Certainly nowadays endemic malaria in Emden, East Friesland, has many points, epidemiologically speaking, in common with malaria in the Romney Marsh, the Isle of Grain, and one or two other places, though the areas are much smaller. On Romney Marsh *A. maculipennis* is abundant and many places exist suitable for it to breed, in spite of an extensive system of drainage. In the autumn and winter the insects can be found in immense numbers in some

of the older cow-byres, stables, pigsties and rabbit-hutches (this may, but does not necessarily, imply zoophilism in preference to anthropophilism, as stated above), but that they are not averse to biting man is shown by the fact that people in these districts use mosquito-nets

It is incredible that the mosquitoes have no opportunity of carrying malaria, for within easy distance there are barracks and concentrations of soldiers, many of whom have been abroad and some certainly carry the parasite. Moreover, endemic malaria does occur both in Romney Marsh and the Isle of Grain. The reasons usually credited with the practical dying out of malaria in districts formerly notoriously malarious are general factors such as higher standard of living, better housing, improved sanitation, and doubtless these are largely responsible, but there has also been improvement in the housing and stabling of cattle and other animals. Anopheles, whether zoophilic or not, are rarely found in the modern light and airy cowsheds, with their clean whitewashed walls, good drainage and free ventilation, whereas in the older dark, damp and stuffy byres and stables which still exist on some of the farms they are present.

So in Emden, the stables, stalls and byres being situated close to the dwellings occupied by man, there would be far more likelihood of success in coping with malaria if attention were given to the housing of animals rather than to attempts to do away with breeding-places which are numerous and extensive. Chatenoud notes that indigenous malaria occurs in north-eastern France and that when he was writing, in 1917-18, twelve *départements* were affected with a mild form of benign tertian, and Roubaud reported Anopheles in the Yonne district and in the environs of Paris and said that they were readily infectible with malaria.

Enough has been said of Italy and we cannot dwell longer on malaria in Europe, suffice it to add, in conclusion, that as recently as 1923 the Red Cross in Russia reported that there were some 3,000,000 cases in the Republic west of the Urals. In Georgia one-half of the population is affected and at the village of Sambourtales, near Tiflis, two-thirds of the total population have died of malaria.

Turning next to Africa we find that without doubt malaria is the chief disease of the whole continent. As recently as 1929 an epidemic arose in Natal and Zululand and continued for six years. Attempts were made to control it by larvicides combined with widespread administration of quinine, but fruitlessly, and a campaign was taken up to attack the adult mosquitoes because it was found that both *A. gambiae* and *A. funestus*, the two chief

vectors, were almost entirely house-frequenters and most infected insects were found indoors. In both Natal and Zululand there are large tracts occupied by but a scanty population, and antilarval work is difficult, and since the rainfall may be high and the extent of exposed water great the cost of larvicidal measures is prohibitive. Attacking the adult insects was cheaper and also more acceptable to the people since it did not touch their water-supply or that of their cattle. Moreover, antilarval work in native reserves is fraught with difficulty, the natives may be induced to carry out some minor drainage round the kraals, but they will not keep it up. Planting of trees, *Eucalyptus saligna* and other species, was advocated and transplants were given to owners of kraals, but success with them was not remarkable. The campaign was carried on as thoroughly as possible. Breeding-places of *A. gambiæ* were located extensively in the winter and dealt with, in the spring more intensive search was made for larvæ and the huts searched for adults. No attempt was made to deal with large areas such as river-beds. By June 1933 all the breeding-sites were located and kept under observation and thereby knowledge was obtained as to where outbreaks might be expected, as soon as the mosquitoes were found to be invading the huts spraying was started. When mosquito breeding is restricted or cost is a minor consideration antilarval measures are very effective, but in Natal and Zululand as stated the area was not restricted. Hut-spraying not only cost about one-third that of antilarval work but was actually more effective. The chief foci were on the coast, the immediate hinterland, in the native reserves and the river-valleys. The administrative details do not concern us.

Introduction of malaria into the highlands of Kenya occurred probably in comparatively recent times and the spread of the disease is attributed to immigration of Europeans and to the consequent increased movement of natives travelling to and from work on the estates, by railways, and so on. In the early 'twenties mosquito-nets were not necessary in the higher parts of Nairobi and malaria was not common in the native reserves at that altitude. In Kikuyu Province where transport facilities are good, the higher and healthier areas are being invaded by malaria.

Malaria in the African native living in a hyperendemic village area causes little sickness. In Taveta, near the Tanganyika-Kenya border, the natives inhabit a strip of forest which is a hyperendemic area (according to P. C. C. Garnham). By the time they are five months old some 85 per cent of the infants are infected and by the sixth month all of them, nevertheless

they appear well nourished and healthy. Most of the infections are subtertian or quartan, benign tertian is rare. Thirty per cent of young adults and 26 per cent of the older were found to be harbouring parasites.

Many have observed how little those living in a hyperendemic area in Africa show in the way of clinical signs. Babies during the first month are fat and placid and their blood is usually free from parasites, in the next two months they become fretful, peevish and ill, their hæmoglobin falls to less than half, the spleen enlarges and may reach the level of the umbilicus. During the succeeding six months a few die, but in the majority improvement sets in, though the blood contains parasites. For about eighteen months, the period of acute infection, there is an average of 7000-8000 per cubic millimetre (there may be as many as 20,000), the condition remains about the same for a couple of years, but after six months there seems to be but little danger to life. During the third year to the fifth they play about as if nothing was wrong, although 80-85 per cent of them have enlarged spleens.

The effects of malaria in children, though not very obvious clinically, are not negligible. The population generally is weakened, abortions are relatively more common and neonatal mortality is high. Hehir, speaking of malaria in India, says that there are 800,000 cases of abortion annually in Bengal, of which 302,400 are due to malaria (written in 1920). The following are some of the figures of prevalence in children in different parts of the tropics. In India numbers are very variable, ranging between nil in Calcutta, Darjeeling Hills and one or two other places, and 86 per cent in Bodawalasa (Jeypore State), in Nagrakata (Duars district) it is 72 per cent. In the Belgian Congo 85 per cent of the native pupils in Stanleyville were infected, their ages ranged from five years upwards. In the Cameroons the parasitic index in children under fifteen years was 75, in Senegal 90 (in 1923), in Nigeria 78 (in 1928), and 24 per cent in infants under twelve months, in Kenya Anderson found the parasitic index in the Terta district to be 60 and the splenic index 90 per cent. Garnham in the Kisumu district found the latter to range between 5 and 45 per cent.

More research is needed before we can speak knowledgeably of malaria in Africa. We do know that it constitutes an economic handicap, but there is need for further study to find out whether there are different races of the common vectors, *A. gambiae* and *A. funestus*, to study their biology and ecology and what part each plays in propagating infection. Many points are still obscure, an open *vlei*, a flat swamp, covered with grass may be harmless,

but a borrow pit in the same *vlei* constitutes a menace, perhaps clearing of the *vlei* from bush allows *gambæ* to find conditions suitable for breeding. As in Malaya and India there are harmless swamps and jungle, so in Africa some swamps there are, even in a district intensely malarial, which appear to be harmless and those living near by are not attacked.

The generality of people hardly realize even now the terrible havoc that malaria works. That it can reduce a prosperous city to desolation is well exemplified, to give a single instance only, in the history of Goa. Goa is now a mass of ruins overgrown with luxuriant vegetation, with a population under a hundred, and only half of these permanently resident, it once had a population of 300,000. De Mello and Bras de Sà paid a visit there in 1935 and found the place full of abandoned wells and pools—they counted some 300—many of them concealed in ruins and undergrowth. St Francis Xavier is buried there and consequently it is visited by pilgrims from all parts of the world. *A. listoni* and *A. varuna* breed there in millions and the place is a well-known haunt of malaria of a malignant type.

We have referred already to Mauritius at the time of its first outbreak in 1866, it is a good example of the deadliness of malaria when it attacks a non-immune people. A short account of the disease from that time to the present is of considerable historical interest. Mauritius lies in the Indian Ocean, 500 miles from Madagascar, 934 from Seychelles, 1300 from Natal and 2300 from the Cape of Good Hope. It has an area about equal to that of Surrey. The low-lying seaboard rises to a central plateau, at a height of 1200 feet, which constitutes one-fifth of the total area. There are three ranges of hills and the rainfall is peculiarly localized, perhaps because of this. It is volcanic in origin and the subsoil, as Dr Balfour Kirk (from whose account this is largely taken) aptly describes it, "resembles a huge bath-sponge containing cavities ranging from tiny pores to caverns as large as a dwelling-house." In other parts the subsoil is less pervious and on the coast are large marshy areas.

Of the three islands of the Mascarene group—Réunion, Mauritius and Rodriguez—the last is the only one on which *Anopheles* is not found. There is little doubt that on the others this mosquito was introduced either from Madagascar or from the mainland of Africa. At present there are four species, namely *costalis* (*gambæ*), *maculipalpis*, *funestus* and *mauritanus*, the last being the chief vector in Mauritius. The first indigenous outbreak occurred at the end of 1865 in Petite Rivière, Black River district,

and spread north and south, and in January 1866 reached Port Louis. The following year it appeared again in the low-lying country and this time spread into the interior. In 1867 more than one-fifth of the population of St. Louis died, from malaria alone. Among a population of 87,000 there were 934 deaths during the last three months of 1866 and 21,023 up to the end of September 1867, or 25.2 per cent of the entire population in the twelve months. At that time there was no quinine available. Up to then Port Louis and Pamplémousses were the residential districts, but the epidemic drove people thence and led to the development of the central plateau as the residential area. Till 1906, or for forty years after the first outbreak of malaria, the disease hardly extended beyond the level of 600 feet, but in that year began to invade the higher altitudes. In 1900 de Grandpré and de Charmy, two entomologists, had determined that the range of malaria prevalence coincided with the distribution of *A. gambiae* and in 1907 Ross, accompanied by Major C. E. P. Fowler, R. A. M. C., visited Mauritius to study the question and advise on preventive measures. Their report is almost a classic now. There is no need to give details of their recommendations, but the main features of their plan were four: 1. Taking periodically a spleen census of children in schools and on estates, and treatment of such as had enlargement. 2. Protection of houses against mosquitoes. 3. Mosquito reduction by both minor and major works. 4. Establishment of an antimalarial organization which should furnish a report annually showing the prevalence of the disease and the progress of antimalaria measures.

As usual, the early enthusiasm concurrent with and for a short time subsequent to Ross's visit began to wane and practically the only measures persisted in were drainage and canalization. Although under section 3 'minor' works were placed before 'major,' the former were disregarded and the Government was blamed when malaria was not eradicated, although one of the chief causes was domestic breeding of *Anopheles*. Conditions remained unsatisfactory and in 1921 Sir Andrew Balfour was asked to visit and advise. At his recommendation M. E. MacGregor, an entomologist, was sent out and he stayed in Mauritius for a year studying the entomological side of the problem. His advice was the establishing of a special Antimalaria Department, with entomologists and engineering, financial and clerical branches. A systematic campaign was initiated in 1927, but was very costly and its activities had of necessity to be curtailed at the time of the world economic crisis. Coming to the present day, the position is roughly

this In Port Louis the municipal water-supply is considerably above the requirements of the population—more than a hundred gallons a head per day There are no industries needing a large supply and much water is wasted, from general waste and leaking pipes In dry weather the rivers may be reduced to a succession of pools wherein *A. gambiae* finds ideal breeding-places (We shall see later how drought led to the great Ceylon epidemic of 1935) On the other hand, heavy rains and the hurricanes to which Mauritius is exposed undo much that has been accomplished, tearing up sections of canalization, obstructing the outlets with gravel and silt, and flooding the town, again providing *A. gambiae* with breeding facilities Attempts have been made to deal with these floods by means of circumvallatory drains, but owing to the friability of the soil the results have not come up to expectations Other recommendations include the erection of dams to direct the flood water to lakes on the lower levels, avoiding the town, and discharging by sluice gates, this, however, has not passed beyond the stage of suggestion and is at present prohibited by the cost

In the coastal lowlands the population live scattered in villages, there is a good deal of marshland and much breeding of *A. gambiae* There is need here for more cultivation and the application of bonification and agriculture which have proved their success in the similar conformation of the Agro Romano In the Central Plateau district much can be done, the people are of the better class, the houses well constructed, there is a good dry season and mosquito control should present little difficulty Under the present organization surveys are undertaken and breeding-places of mosquitoes are noted, permanent breeding-sites are eliminated, where possible, careful surveillance made of water collections, and there are legislative measures making householders liable for domestic breeding foci, but, like most of such enactments in the tropics, these are more honoured in the breach than in the observance

We see, therefore, that the prospect of effective control in coastal regions is remote and malaria is likely to remain endemic there for years In Port Louis the main problem is how to deal with the flood water and only major works of an engineering nature can do this In the Central Plateau all that is needed is co-operation on the part of the residents, otherwise the complaint that "in spite of vast sums spent by the Government on major works the morbidity from malaria in this region is practically unaffected" will continue to find expression

Two other outbreaks of comparatively recent date have acquired

sufficient notoriety to be of historical importance, namely, those of Barbados in 1927 and Ceylon in 1935

Alleyne, the Port Health Officer of Barbados, was of opinion that *Anopheles* had always been present in the island but had eluded discovery. If so, it is strange that, with ships so often visiting there whose crews must have contained men carrying infection, the place did not become notorious like the West India islands in general. On the other hand, Ballou, the entomologist, in the course of seventeen years' investigation could not find them, nor did G. C. Low who looked for them at the beginning of the present century. When malaria appeared in 1927 Seagar made a survey and found them without difficulty breeding in temporary pools and more abundantly in those nearer to the schooner moorings. Two or three months later a further survey showed that the mosquitoes had extended their range, the permanent waters were infected and breeding was going on right across the island. Many years before Balfour had suggested 'trap pools,' but the advice was disregarded. The outbreak was ascribed to infected mosquitoes brought in the holds of small trading schooners and to the return of infected labourers from Cuba.

The Ceylon epidemic, one should say the last Ceylon epidemic, of 1935, for history indicates similar outbreaks having occurred in previous years at intervals, needs no long description. It has been fully detailed in papers, medical and lay, and at the time called forth much discussion. Five years earlier the Government Entomologist, H. F. Carter, had given a warning regarding the south-western lowlands. He stated that approximately three-fourths of the low country of Ceylon was severely malarious, while the remaining fourth, stretching from Colombo 22 miles north, 100 south and 30 inland, was not, although from the physical and climatic points of view conditions seemed to be favourable. Probably, he said, *A. culicifacies* and *A. funestus*, mosquitoes prevalent in more malarious districts, are uncommon in these south-western lowlands. But, though scarce, they are a constant menace since conditions may arise which favour their increase. Epidemics had occurred before in certain localities associated on the one hand with importation of labourers and on the other with prolific breeding of *A. culicifacies* in quarries or in constructional works. Conditions referred to above, favouring increased breeding of this mosquito, arose in 1935.

The outbreak was due primarily to failure of the north-west

monsoon From May to October there was drought instead of the usual summer rains The north-eastern parts of the island are not reached by this monsoon, even in normal years, so the failure in that year would have no effect there and, in fact, malaria there was no worse than usual In the south-west districts, on the other hand, the large lakes dwindled to a collection of small, shallow ponds, the larger rivers became merely a series of pools As a result, breeding-places for mosquitoes were hundreds, nay thousands of times as many as in normal seasons, and these insects became a veritable plague, *A culicifacies* swarmed into the houses The infection rate of those caught in the houses over the whole region was 14 per cent

Nor was this all, the prolonged drought led to the failure of the crops and to consequent poverty and undernutrition, and, further, malaria being ordinarily not very rife in this area, there was a large non-immune population Records of previous epidemics were, of course, less complete than those of this one, but this was certainly the worst recorded in the history of Ceylon The outbreak started in October, by November many of the dispensaries were treating ten times the usual number of cases, by the middle of December the epidemic was at its height and whole villages were struck down at a time and the roads were blocked by the victims painfully making their way to hospitals and dispensaries which had been set up Even with unlimited funds and a large staff it would be difficult to take adequate steps to deal with such a disaster at short notice To control malaria in a plantation or a small town is a very different matter from suppressing mosquito breeding in thousands of pools in the beds of large rivers and their tributaries and in lakes and marshes The medical department at one time was treating as many as 60,000 patients a day The first wave of the outbreak came to an end in the following March, but was soon followed by a second wave, apparently not fresh infections but recurrences In the seven months 80,000 deaths from malaria were recorded

Those who gauge the ill effects of malaria merely from the official returns of the number of cases recorded, the mortality and invaliding from this cause—and there are many who do—have no true conception of the position, the evil is of far greater extent

For an example let us consider India In the Records of the Malaria Survey for 1935 (September–December) and 1936 (March) Colonel Sinton has gathered together some most instructive information on *What Malaria costs India, Nationally, Socially and*

Economically In assessing this there are many things to be taken into account, mere enumeration will suffice to indicate the complexity of the question and it will be seen that some of the items cannot be estimated with any approach to accuracy. How, for example, can we gauge the value of work which a malaria-stricken people has to leave undone, or the loss resulting from work being badly done? The cost of medicine, of invaliding, of death and funeral expenses, of medical attendance, this can be estimated perhaps and they make a large total. But this is far from covering the whole, the effects are much more widely felt. There are the effects on the natural increase of the population, in this regard mention has already been made that some 300,000 abortions due to malaria occur annually in Bengal alone, secondly, there are the effects on the health and vitality of the people, indirect as well as direct, malaria is believed to be responsible thus for at least 2,000,000 deaths annually in India. The report contains a quotation in connection with the deleterious influence of the disease on the physical development of children and adults, a quotation which from its felicitous aptness is probably American (the source is not given)

Every once in a while somebody rises up to criticize modern parents for devoting too much time to their children's physical being (as compared with their spiritual and educational). Our righteous ancestors disregarded their bodies and paid attention to their souls, and it might be added that by neglecting their bodies in the interests of their souls, they beat us to heaven by an average of twenty years.

8 TREATMENT

We come now to the history of the treatment of malaria which means the history of cinchona, for other forms of treatment, particularly modern synthetic chemotherapeutic compounds, are still in the melting-pot and the many nostrums which have had an ephemeral existence of a few months need no more than a passing reference, they are unworthy of a place in history. The story of Cinchona contains much of real romance in the course of three to three and a half centuries during which it has been in use.

Of treatments in early days, prior to that with cinchona history has little recorded and the only one which had any wide vogue was the *spider treatment*, the arachnid being either carried as a talisman, or applied locally or taken internally.

Sir Kenelm Digby gives the advice to a friend to "carry live spiders in a box to soak up the pestilential vapours," and the lines

of Longfellow in *Evangeline* refer to this as a well-recognized charm

Only beware of the fever, my friends, beware of the fever !
For it is not like that of our old Arcadian climate,
Cured by wearing a spider hung round one's neck in a nutshell

Probably the nutshell played an equal part with the spider it enclosed so far as the prophylaxis of malaria was concerned, and the principle has its modern analogy in the carrying a raw potato in the pocket as a preventive of further attacks in those subject to rheumatism, or carrying a nutmeg and occasionally nibbling at it to ward off boils—procedures much more widespread than educated people believe—and even more modern still the wearing of a locket containing iodine as a preventive of influenza

Some of the older writers considered spiders more effective in malaria when they were applied in the form of a plaster, others again considered that they acted with any certainty only if they were dried, powdered and taken internally Ireland went one better, for it was the opinion there that only spiders swallowed alive were efficacious In India spiders' webs made into pills were valued in the treatment of this disease

Reference may be made here, in order to save returning to the question, to a measure, not for personal protection but for prevention on a more extensive scale, a method of control, which was in the public eye a decade or so ago and obtained for a time a degree of authoritative support, with very little scientific foundation, namely, the planting of clover Willcox in 1927 wrote "There must be something in all leguminous plants, especially in certain kinds of clover, which makes mosquitoes immune from malaria" d'Herelle stated that in all malaria-free regions of the Argentine there is a scented clover, *Melilotus altissima*, whose blossoms are frequented by the malaria mosquitoes which feed on the syrup *coumarin* and he asks "May not this act on the mosquito as does quinine in man?" Certainly the introduction of *Melilotus* has coincided with expulsion or disappearance of malaria from certain islands of Zealand and from the northern provinces of Holland All this may be, nay is, very plausible but in reply to d'Herelle's question Bruce Mayne has demonstrated that coumarin has no plasmocidal value in mosquitoes Further, in the delta of the Mississippi, when the cotton plants were ruined by the boll-weevil, alfalfa, a legumen, was substituted for it, but the people living near are not protected by the presence of alfalfa from attacks of malaria Alfalfa will not grow in a

water-logged soil and wherever a decline in malaria coincides with planting of alfalfa this decline is due probably to the drainage necessary for the proper cultivation of the legume, just as it did with the introduction of *Melilotus* into Holland

The history of cinchona contains much of romance, not in the modern sense of untrue, or exaggerated, but in its original implication of suggesting fiction by its strangeness and interest. First, as regards the name. Linnæus, about 1740, named the plant after the Countess of Chinchona, but, acting on erroneous information he called it *Cinchona* instead of *Chinchona*. The name 'quinine' is said to be derived from 'quina,' the Spanish way of spelling the Peruvian word 'kina,' that is 'bark'. For the following account of the history and lore of cinchona we are indebted largely to Dr C J S Thompson, formerly of the Wellcome Historical Museum and to Clements Markham's book on the life of the Countess. Not a little that is legendary surrounds its early history, the manner in which its medicinal properties were discovered—a drug "the most precious of all those known in the Art of Healing". La Condamine records in 1738 that its properties as a febrifuge were discovered by the natives of Peru watching the pumas chew it to cure their fever. He does not state how the natives ascertained that the pumas (in another record the pumas have become lions) were suffering from fever, nor is it improbable that they were unaware that a puma's normal temperature differs from that of man and they certainly had no means that we are acquainted with of measuring it, the handy clinical thermometer dates from the days of Clifford Allbutt. The story of an Indian exhausted with fever collapsing and falling down at the edge of a lake, drinking of the water into which a cinchona tree had fallen and awaking free from fever is quite possible. If his infection was benign tertian or quartan he would naturally be afebrile the following morning whether he drank the cinchona water or not, but, unfortunately for its truth as being the first mode of discovery, the properties of cinchona were known at least a century before the time of which this story is told.

The earliest knowledge on which we can rely is that in 1600 a Jesuit missionary, working at Malacotas, south of Loxa, Peru, suffered from an attack of intermittent fever and was cured by the bark given to him by an Indian chief. Some quarter of a century later the Spanish Corregidor (in our parlance, Mayor) of Loxa, Don Lopez de Canizares by name, was similarly cured. Incidentally, its value is designated in its name *Quina-quina*, i e

Bark of barks Nevertheless, later the Peruvians did not make very extensive use of it, Poeppig, writing in 1830, states that Huanuca people who suffered much from ague were averse to taking it, while the natives of Loxa where the first authenticated account of its use was found considered it as a dangerous drug Also the natives of Ecuador and Colombia, though they used the 'red bark' as a dye, would not be persuaded that it had any other virtues

The foregoing, if not actually legendary, has not emerged far from the nebulous Let us pass on to what is really historical

Ana de Osorio, daughter of the Marquis of Astorga, married at the age of sixteen years Don Luis de Velasce, who was a grandson of the first Marquis de Salinas On the death of Don Luis four years later his widow became lady-in-waiting to Queen Margaret, wife of Philip III Before long she was married again, this time to Count Chinchon, whose estate, Chinchon, was near Madrid In 1628 he was appointed Viceroy of Peru and he and his wife, early in January the following year, entered Lima in state The Countess suffered from fever and, hearing of this, Don Francisco Lopez, the Corregidor of Loxa spoken of above, sent a packet of the powdered bark to her physician, Juan de Vega. Its administration was followed by rapid and, we are told, complete recovery

Aegrotebat in Civitate Limensi quae est Metropolis Regni Peruviae, Uxor Proregis, qui tum temporis erat Com del Cinchon eratque morbus ejus Tertiana febris Rumor hujus aegritudinis per Urbem statim vulgatus, ad finitima quaeque loca pervasit, Loxamque usque tenuit Praefecturam tum agebat eo loci Hispanus homo,

qui de Comitissae aegritudine certior factus, deliberavit per Litteras maritum Proregem admonere, quod postea fecit, in arcanis scribens, sibi esse Remedium quoddam quo si ita voluisset Prorex, sponsor indubius ei erat, convalituram ejus Uxorem febrigue omni liberandam

Quibus auditis, deliberatum est de sumendo Remedio, quod sumpsit et mirum dictu, dicto citius convaluit, stupentibus omnibus (Sebastian Bado Anastasis corticis Peruviae seu Chinae Chinae defensio Seville, 1663)

The species of bark was that of Cascarilla de Chaluaguera which contains a high proportion of cinchonidine Enthusiastic at the success following its use in her own case, the Countess ordered the bark to be gathered in quantity, administered it to her dependants, recommended it to her friends and distributed it widely to any with fever, just as ladies nowadays recommend and distribute patent medicines in which they have faith—history repeating itself In a short time it came, for this reason, to be called the 'Countess' Powder'

Nec tam deferri jussit magnum Remedium, scilicet Corticem quam voluit illud suis manibus dispensare frequentibus aegrotantibus
Et hinc factum, ut is Cortex *pulvis Comitissae* vocatus

(Ibid)

In 1640 she returned to Spain and because tertian ague was common on her husband's estate, she brought a quantity of the bark with her in the hope that it might prove as beneficial there as in Peru

So runs the story as it is generally believed and thus it has been handed down as history Unfortunately, however, there is an insuperable obstacle to its acceptance F J B Juste published in Madrid in 1934 a work entitled *Historia del Descubrimiento de la Quina* According to his researches Doña Ana de Osorio y Manrique, the wife of the Count of Chinchon who was Viceroy of Peru from 1629 to 1639, cannot have been the Countess referred to as cured by use of the bark because her death took place in Spain on 8th December, 1625, that is four years before the Count was appointed Viceroy It may have been the Count's second wife, Doña Francisca y Enriquez de Rivera, whom he married in 1628 She died at Cartagena (Colombia) on 14th January, 1641, and Juste could find no record of her visiting Europe between 1629 and 1641, though she may have done so when her husband's viceregal term ended in 1639 If she did, and the historical report generally accepted mentions the Countess returning to Spain in 1640 (the second wife being mistaken for the first), we have no explanation for her return again to South America (Colombia) where she died in the following year It may be that Cartagena 'Colombia' is a mistake and that the place of her death was Cartagena in Spain and it may well be that she went to this coast town for her health, Cartagena being barely 200 miles distant from Chinchon, an inland town near Madrid In whatever way we regard it, it may be *ben trovato* but *non è vero*, at all events not *tutta la verità*

Dr de Vega, her physician, returning soon after the Countess, also brought a supply and either the Hippocratic oath was not taken by Spanish doctors of that day, or avarice led him to break it, anyway he sold his powder in Seville at 100 reals a pound

Thirteen years later its fame had spread, for in 1653 Chifflet, physician to the Archduke Leopold of Austria, who was Governor of the Low Countries, wrote that it was one of the wonders of the day, the tree growing in the Kingdom of Peru, called *Lignum Februm*, whose virtues chiefly reside in the bark which is known as *China Febris* During the last few years it has been imported into Spain and thence sent to the Jesuit, Cardinal Joannes de Lugo at Rome

Juan, Cardinal de Lugo was born on 25th November, 1583, in Madrid. He was made a Cardinal on the 14th December, 1643, by Pope Urban VIII, and died on 20th August, 1660.

The Archduke had taken it for two attacks of fever the previous year, but refused it in a later attack and, deservedly, died. In a subsequent controversy some medical men held that though it relieved the fever it 'fixed the humour' and caused relapse.

In 1659 a Louvain doctor, Roland Sturm, in a treatise on its use, said that in Antwerp and Brussels it went by the name *Pulvis jesuiticus*. The Jesuit Fathers gave it free to the poor, but charged its weight in gold to the wealthy. Other synonyms of the time were *P. peruanus* and *Peruvianum febrifugum*. It had been sent to Rome, as stated already, to Cardinal de Lugo, by the Jesuit Fathers in Peru, and he gave it to the poor at his palace, hence other synonyms *Cardinal's bark* or *Fathers' powder*. It cost three florins a dose in Paris where Cardinal de Lugo gave it to Louis XIV for an attack of intermittent fever and brought about his recovery. Then, as now, its high price led to worthless substitutes being put on the Spanish market, astringent barks adulterated with aloes to impart a bitter taste being sold as Cinchona. Possibly it was owing to the introduction of substitutes and adulterants that Warren, in a long letter to a friend on the treatment of fevers, wrote in 1733

Nobody who has had but a tolerable share of Practice amongst the Sick can be ignorant that this and the last year's fevers were of a changeable and uncertain Nature, and that the Peruvian Bark quite lost that Force and Certainty of Curing which formerly it was so famous for.

Between 1655 and 1660 ague was rife in England, and Brady, Professor of Physick at Cambridge, prescribed the bark, Jesuits' powder, which had been brought over from Antwerp by a merchant, James Thomson. Of the introduction of cinchona into England Sydenham writes (1680) in his *Epistolæ Responsoræ duæ* *Cortex Peruvianus* cujus *Pulvis Patrum* vulgò nomine insignitur, annis abhinc quinque et viginti (si benè meminì) apud Londinenses nostras in exterminandis Febribus Intermittentibus, maxime Quartanis primum Coepit inclarescere.

Professor Brady in a letter to Sydenham tells him how useful he had found the bark in cases of intermittent fever, but throws doubt on some of the favourable reports of its use, even by physicians of repute in cases of continued fever. Brady was writing from Cambridge, the letter is among Sydenham's *Epistolæ*. He says

In sectione prima, Cap quinto, libri tui paucis egisti de usu Corticis Indici et ejusdem exhibendi methodo Equidem scio quosdam haud infimi subsellii Medicos, qui in magna quantitate et dosi saepius repetitâ eum exhibent Alios item qui ex eodem extracta, infusiones, et ex infusionibus julapia et emulsiones conficiunt, quibus modis se non tantum Intermittentes, sed et continuas quasdem certò curare affirmant Magnum procul omni dubio in Curandis Intermittentibus est remedium Ego quidem per 20 plus minus annos dictum Corticem variâ forma et multiplici praeparatione maxima cum successu exhibendum curavi

Vale, Vir integerrime qui hisce peragendis totam Medicorum turbam meritò divincies, inter reliquos verò,

Tibi jure meritoque amicissimum

R BRADY

Cantabrigiae

Decem 30, 1679

The drug, however, acquired its reputaton in England mainly through Robert Talbor or Tabor (by some written erroneously Talbot) who made his own reputation and incidentally a fortune by exploiting it as a secret remedy Talbor settled in Essex in 1671 "near the seaside where agues are epidemical diseases", probably, one conjectures, Mersea and the marshes His secret remedy, mentioned in his book *Pyretologia a Rational Account of the Cause and Cure of Agues*, published in 1672, contains 'two indigenous and two exotic' ingredients and he artfully pens the warning

Let me advise the world to beware of palliative cures and especially of that known as Jesuit's Powder, as it is given by unskilful hands Yet this powder is not altogether to be condemned, for it is a noble and safe medicine and if rightly prepared and corrected, and administered by a skilful hand, otherwise as pernicious a medicine as can be taken

Talbor prospered and removed to London where his fame led to his being called to Windsor to Charles II whom he cured of an attack of fever To protect him from interference by the College of Physicians on the score of his having no medical qualification, the King had a letter written and sent to the College

Comitus censorius Mai 3, 1678

Missae sunt literae Praesidi a Magno Camerario Dño Arlington

Sir,

His Majesty having received great satisfaction in the abilities and success of Dr Talbor for the cure of agues has caused him to be admitted and sworn one of his physitians has commanded me to signify his pleasure unto you that you should not give him any molestation or disturbance in his practice

I remain your humble servant, Arlington

May 2, 1678

In 1672 he was appointed Physician to the King and later received a knighthood. The adage which speaks of the disagreement common among members of the same profession is exemplified in the following brief quotation from Evelyn's Diary in 1679 (writing from hearsay he calls him 'Tudor')

Conversed with the Marquis of Normandy concerning the Quinquina, which the Physicians would not give the King at a time when he was in a dangerous ague (out of envy, because it had been brought into vogue by Mr Tudor, an apothecary) until Mr Short to whom the King sent to know his opinion of it privately sent word to the King that it was the only thing that could save his life, and then the King enjoined the physicians to give it to him, which they did and he recovered.

Talbor visited Spain and France and is mentioned by Madame de Sévigné when writing of 'the Englishman and his cures'. He successfully treated the Dauphin, son of Louis XIV, for which he was made a Chevalier and induced for 2000 louis d'or and an annuity of 2000 livres to reveal his formula and method, but even then only on one condition that they were not published till after his death—one of the few examples of a man being able to eat his cake and have it. Nevertheless, Louis did apparently make some immediate use of the 'secret remedy' thus confided to him, for in *Lettres édifiantes et curieuses écrites des missions étrangères*, Paris 1781, occurs the following quoted by Professor Stephens in the *Journal of Tropical Medicine and Hygiene* (16th August, 1937)

Pâtes médicinales que Louis XIV faisoit distribuer dans son Royaume, dont les Missionnaires avoient apporté provision en Chine, qui y opéroient des guérisons, et dont l'Empereur se servit lui-même avec succès contre l'avis de ses Médecins, il prit aussi du quinine dans une fièvre intermittente, ce remède étoit inconnue en Chine, et le Prince par confiance dans les Missionnaires, et après en avoir fait faire l'expérience sur d'autres malades, s'obstina à en prendre malgré ses Médecins, et s'en trouva bien, pour en récompenser les Missionnaires François, il leur donna une maison dans son palais l'année 1693.

Depuis deux ans l'Empereur avoit beaucoup examiné nos remèdes d'Europe, et particulièrement les pâtes médicinales que le Roi fait distribuer aux pauvres par tout son Royaume.

Nous lui avions marqué toutes les maladies qu'elles guérissent en France, et il avoit vu par des expériences réitérées qu'elles faisoient en effet des cures si merveilleuses et si promptes, qu'un homme à l'extrémité et dont on n'attendoit plus que la mort, se trouvoit souvent le lendemain hors de danger. Des effets si surprenans lui firent donner à ces pâtes le nom de *Chin-yo*, ou de remèdes divins. La maladie qu'il avoit alors étoit un commencement de fièvre maligne. Quoiqu'il eût par plusieurs exemples certains que les pâtes guérissent son mal, les médecins Chinois

ne jugerent pas à propos de lui en faire prendre, et ils le traitèrent d'une autre manière mais l'Empereur voyant que le mal augmentoit et craignant un transport au cerveau, prit son parti et se fit donner une demi-prise de ces pâtes

La fièvre le quitta sur le soir et les jours suivants il se porta mieux, il eut ensuite quelques accès de fièvre tierce, peut-être pour on s'être pas purgé suffisamment Quoique ces accès ne fussent pas violens, et qu'ils ne durassent que deux heures, il en eut de l'inquiétude

Medicinal Pâtes that Louis XIV had distributed throughout his Kingdom, of which the missionaries had brought a supply to China, which effected cures and which the Emperor used himself with success against the advice of his doctors, he also took some quinine for an intermittent fever, this remedy was unknown in China, and the Prince, from his confidence in the missionaries, and after having carried out trials on other patients, determined to take some in spite of his doctors and found himself well, as recompense to the French missionaries he gave them a house in his Palace, the year 1693

For two years the Emperor had often examined our European remedies and particularly the medicinal 'pâtes' which the King distributed among the poor throughout his kingdom

We informed him of all the diseases which were cured by them in France, and he saw from repeated trials that they effected cures so marvellous and so rapid that a man who was thought to be on the point of death often found himself the next day out of danger Such surprising effects made him call these 'pâtes' *Chin-yo* or 'divine remedies' The disease which he had at the time was at first a malignant fever Although he knew from several definite cases that the 'pâtes' would cure his disease, the Chinese doctors did not think fit that he should use them, and they treated him by other methods, but the Emperor, seeing his illness increasing and fearing it might attack his brain, himself resolved to take a half-dose of the pâtes

The fever left him in the evening and on the following days he was better, he then had attacks of tertian fever, probably because he had not purged himself adequately Although the attacks were not severe and did not last more than two hours, they caused him some anxiety

Cinchona was used medicinally in France before Talbot's visit there, Rolleston concludes that Barbeyrac, a physician of Montpellier, used it in 1664, and S F Geoffroy in his *Tractatus de materia medica* (Paris, 1741) shows it to be no new drug in Talbot's day

Donnec anno 1679 Robertus Tabor vel Talbot Eques Anglus
Kinae Kinae usum sub *Anglici remedi* nomine, vulgo le remède Anglois,
in Galliâ resuscitavit

Tabor again visited Spain in 1680 and cured the Queen of an attack of fever, the next year, 1681, he died in London, at the age of forty years, and was buried in Trinity Church, Cambridge

In 1682 his *Secret for Cureing of Agues and Feavers* was published, giving the details of his cinchona preparations and it may be noted that one of them had the same strength as the present British Pharmacopœia tincture. The book was published first in France with the following title *Le remède anglois pour la guérison des fièvres, publié par ordre du Roy. Avec les observations de Monsieur le Premier Médecin de sa Majesté, sur la composition, les vertus, & l'usage de ce remède* Paris, A Padeloup, 1682. 'Le premier Médecin' referred to was Nicolas de Blegny. Later in the same year the English version appeared, the full title being *The English Remedy or Talbor's wonderful secret for cureing of agues and feavers Sold by the author to the most Christian King, and since his death ordered by his Majesty to be published in French for the benefit of his subjects, and now translated into English for publick good* London, J Hindmarsh, 1682. It was also published in Latin at Ferrara in 1687 with the title *Remedium Anglicum pro curatone februm*, etc.

From the English version may be quoted the following

When in the hands of the Jesuits it [cinchona] was sold in Rome for 8 or 9s the dose, which consisted of two drachms. Three or four years ago the best might be had for 40s the pound. Sir R. Talbor observing that Febrifuges were prepared which came very near his own and fearing that least somebody at length might discover it, resolved to buy up all the Quin-quina that he could find in Paris and the chief towns of England and France.

The reason, be it noted, was that "least somebody might discover" his secret remedy, not for philanthropy because the price had advanced from half a crown to 32-36 shillings. His action must have made it still more expensive.

Thompson in his article speaks of a bill in the British Museum dated 1675, in which Dr Charles Goodal offers for sale at the 'Coach and Horses' in the Physicians' College, Warwick Lane, "a superfine sort of Jesuit's bark, ready powdered and papered into doses, at 4s per ounce." The drug made its first official appearance as *Cortex peruanus* in the London Pharmacopœia of 1677.

Gideon Harvey (who must not be confused with the immortal William) does not seem to have thought very highly of cinchona. He writes in 1683 in *The Conclave of Physicians, detecting their Intrigues, Frauds and Plots against their Patients. Also a Peculiar Discourse of the Jesuit's Bark*

After all, I could wish these Fathers had kept their Indian bark to themselves, and sure I am hundreds would be on this side the Grave, whose Bones are now turned into their first element. If you shall

meet with a Physician, that can safely and not over speedily Cure you without giving the Jesuits Powder, never meddle with the Jesuit, with whom the less a man has to do either sick or well, it's the better . In fine, the effects appear so miraculous to many that they imagine the Jesuits by Imprecations, by Exorcisms and Charms on their Bark, have made use of their Cloven-footed Master

(Quoted by J W W Stephens)

Drs Wong and Wu, in their work the *History of Chinese Medicine*, state that cinchona is first mentioned in China as effecting the cure of the Emperor Sheng-tsu (K'ang Hsi) when he was suffering in 1692 from an attack of tertian ague Their authority is Du Halde, the author of *Description de l'Empire de la Chine* De Maille in his *Histoire Générale de la Chine* gives the date as April 1693 This latter is more probable because Père de Fontaney was in Canton at the end of 1692 and the drug was not administered until after his return to Peking and on the 4th July, 1693, the Jesuits received great reward from the Emperor This is probably the case referred to in *Lettres édifiantes et curieuses*, already mentioned, but there is nothing to be found regarding the cure in the Tung Huahu or K'anghsi Shih-lu The quotation in the *Lettres édifiantes* (the original spelling and accents being retained) in respect of this case is as follows

On en étoit là, lorsque nous arrivâmes à la Cour le Père de Visdelou et moi Nous apportions une livre de quinquina, que le Père Doln, plein de charité pour nous, nous avoit envoyé de Pondichéry Ce remede étoit encore inconnu à Peking Nous allâmes de presenter comme le remede le plus sur qu'on eut en Europe contre les fievres intermittents Les quatre Seigneurs, dont nous avons parlé, nous reçurent avec joie, nous leur dîmes la maniere dont il falloit le préparer et s'en servir conformement à l'imprimé fait en France par ordre du Roi Ils ne contenterent pas de cela, ils voulurent sçavoir d'on venoit le quinquina, quels en étoient les effets, quelles maladies il guérissoit, comment le Roi l'avoit rendu public pour le soulagement de ses peuples, après avoir donné à celui qui avoit le secret une récompense digne d'un si grand Monarque

On fit le lendemain l'expérience de ce remede sur trois malades On le donna à l'un après son acces, à l'autre le jour de l'accès, et au troisieme le jour qu'il avoit du repos Je ne sçais si Dieu voulut faire paroître sa puissance en cette occasion, ou si ce fut un effet naturel du remede Ces trois malades qu'on gardoit à vu dans le Palais furent guéris tous trois des cette premiere prise On en donna avis sur le champ à l'Empereur, qui aurait pris ce jour-là même du quinquina, si le Prince héritier, qui étoit extrêmement inquiet de la maladie d'un Pere qu'il aime tendrement, n'eut craint quelque mauvais effet d'un remede qu'on ne connoissoit pas encore Il appella les Grands et leur fit des reproches d'en avoir parlé sitôt à l'Empereur Ceux ci s'excuserent modestement, mais pour montrer qu'il n'y avoit rien à craindre (car de tout ce que nous leur avions raconté, ils avoient jugé que le quin-

quina faisoit aucun mal) ils s'offrent tous quatre d'en prendre et le Prince y consentit. Incontinent on apporta des tasses avec du vin et du quinquina, le Prince fit lui-même le mélange, et les quatre Seigneurs en prirent devant lui, sur les six heures du soir. Ils se retirèrent ensuite et dormirent tranquillement, sans ressentir la moindre incommodité.

L'Empereur, qui avait fort mal passé la nuit, fit appeler sur les trois heures du matin le Prince *Sosan*, et ayant appris que lui et les autres Seigneurs se portoient bien, il prit le quinquina sans délibérer davantage. Il attendoit la fièvre ce jour là, sur les trois heures après midi, mais elle en vint point, il fut tranquille, le reste du jour, et la nuit suivante. L'Empereur continua tous les jours suivans à prendre du quinquina, et à se porter mieux de jour en jour.

Such was the state of affairs when Father de Visdelou arrived at the Court. We had brought with us a pound of quinquina that Father Doln, full of charity towards us, had sent us from Pondichery. This remedy was still unknown in Peking. We proceeded to offer it as the surest remedy known in Europe against intermittent fevers. The four Mandarins, of whom we have spoken, received us with joy, we told them how it should be prepared, following the printed instructions ordered in France by the King. They were not content with this and wanted to know whence quinquina came, what were its effects, what diseases it cured, how the King had made it public for the relief of his people, after having given to the person who held the secret a recompense worthy of so great a monarch.

The next day the remedy was tried on three patients. It was given to one after his attack, to another on the day of his attack, and to a third on a day during the interval between attacks. I do not know whether God wished to show His power on this occasion, or whether it was a natural effect of the remedy. These three patients who were under observation in the Palace were cured, all three after the first dose. News was immediately brought to the Emperor, who would have taken quinine that same day, had not the Crown Prince, who was much troubled by his father's illness and whom he loved dearly, been afraid of some bad effect of a remedy that was as yet unknown. He called the Mandarins and reproached them for having spoken so soon to the Emperor. They excused themselves modestly, but to show there was nothing to fear (as from all we had told them they believed that quinquina was not harmful) they offered, all four of them, to take some and the Prince consented. Forthwith cups were brought with wine and quinquina, the Prince himself made the mixture, and the four Mandarins took it in front of him, at six o'clock in the evening. They then retired and slept peacefully without the least inconvenience.

The Emperor, who had had a very bad night, called for Prince *Sosan* at three in the morning, and having learnt that he and the other four Mandarins were quite well, he took some quinquina without more ado. He expected the fever that day, about three in the afternoon, but it did not occur, he was well the rest of the day and the following night. The Emperor continued to take quinquina daily and to get better from day to day.

La Condamine, in 1743, was the first to attempt transport of the plants to Europe with the help of de Jussieu in Peru who, after many difficulties in acquiring the plants, was robbed of his collection by his servant under the impression that the boxes contained money or specie de Jussieu became insane In his honour one variety of *Cinchona calisaya* was called *C josephiana* (his Christian name was Joseph)—not a very satisfying compensation

The Peruvians were reckless in collecting the bark and destroyed so many trees in the process that there arose a fear of shortage and efforts were made to cultivate the trees elsewhere, notably in India in the middle of the nineteenth century, and by the Dutch in Java The *Encyclopædia Britannica* states baldly

The bark was formerly procured by cutting down the trees which grew isolated or in small clumps in the dense forests of New Granada, Ecuador, Peru and Bolivia Cultivation was first tried in Algeria, but failed Later, in 1854, the Dutch Government fitted out an expedition to South America and obtained several hundred trees which were planted in Java A British expedition to the Andes in 1859 brought back trees which were planted in Ceylon and India The cultivation was at first on a large scale and was very successful in Ceylon, but the decrease in price of quinine and the attacks of disease caused it to be given up there

As a matter of fact the story is more romantic than this Charles Ledger, a London merchant of Bucklersbury, was buying alpaca in South America for the New South Wales Government when a native servant succeeded in procuring for him some seeds of *C calisaya* The natives, enraged with jealousy, killed him

He had, however, already forwarded the seeds to his brother in England who offered them to the British Government Characteristically, the offer was turned down and the vendor sold half to the Dutch Government for £33 and half to a planter in Ceylon The former raised in Java some 20,000 plants and the great industry bringing untold gold was founded

The first scientific study of cinchona was made in 1845 when the botanist Weddell was sent from Paris, where he was working in the *Muséum d'Histoire naturelle*, to investigate the trees in Peru and Bolivia He identified several species and noted how much the natives had destroyed trees by their intensive exploitation so that forests had been almost devastated Weddell brought back to Paris several species for growing in the Jardin des Plantes In 1850 some *C calisaya* were trans-shipped to Java and became the source of a more extensive cultivation there, the soil being favourable This *C calisaya* was really a hybrid of the true

C. calisaya and *C. succirubra*, the former yielding yellow quinine, the latter red. It was called *C. ledgeriana* from the man spoken of above who collected it in Bolivia.

Until early in the nineteenth century the bark was used in a crude state. In 1810 (some say 1815) Gomez of Portugal isolated a substance which he called *cinchonine*. Ten years later, in 1820, two French chemists, Pelletier and Caventou, showed that this contained two alkaloids, named by them *quinine* and *cinchonine*. Subsequently other principles were isolated: *quinidine* in 1833 by Henry and Delondre, and *cinchonidine* in 1844 by Winckler, though the French claim that Pasteur isolated this in 1853. Altogether more than a score of alkaloids have been found in cinchona barks and their derivatives are many, for example, quinine, first employed as the sulphate, has been replaced by the bisulphate, the hydrochloride, the bihydrochloride and the hydrobromide, on account of their readier solubility and less toxicity, but these are matters rather of pharmaceutical than of historical interest in the sphere of tropical medicine.

The four above mentioned, quinine, quinidine, cinchonine and cinchonidine, are the crystallizable alkaloids. What is known in India as cinchona febrifuge is a mixture of alkaloids remaining after the manufacture, *plus* a certain proportion of quinine. Standardized cinchona febrifuge goes by the name totaquina and this contains 70 per cent crystallizable alkaloids, 15 per cent at least of which is quinine, and not more than 20 per cent amorphous alkaloids. There are two types: (i) made from *C. succirubra* and *C. robusta*, of which the chief alkaloids are quinine and cinchonidine, (ii) made from *C. ledgeriana* which is chiefly cinchonine. This type is the residue of mixed alkaloids after extraction of quinine from the *ledgeriana* bark, to which quinine is added to constitute at least 15 per cent of total crystallizable alkaloids. It is a brown powder, hardly at all soluble in water, but readily in dilute acid. According to analyses made at the Institute for Medical Research, Kuala Lumpur, Federated Malay States, its percentage composition is approximately quinine 19, cinchonidine 3, cinchonine 50, quinidine 3. Crystallizable alkaloids constitute about 77 and amorphous alkaloids 15 per cent. The former, Totaquina I, is more active, probably because it contains more quinine.

In 1829 questions arose regarding the quality of quinine or of the bark coming from certain parts of Peru. Some of those who used it said that it had the qualities of cinchona but contained no quinine. Pelletier was instructed to undertake an

analysis of it and, with his colleague Coriol, examined specimens of the cortex sent from the port of Arica on the Peruvian coast. They reported that this bark contained no quinine but a new alkaloid which they named *aricin* from its place of origin. On this report its introduction into Europe ceased and in 1873 Hesse expressed doubt as to the existence of any such alkaloid. Four years later, however, he had an opportunity of analysing more samples and found *aricin* present in a proportion of 0.62 per cent.

More recently Moissan and Landrin, in 1890, extracted 3-3.5 per cent of *aricin* from specimens of cinchona bark. There is no published account of the use of this alkaloid in the treatment of malaria, but a detailed account of its physiological action on the circulation—it lowers arterial pressure—was published by Raymond-Hamet in 1938 (*Bull Acad Méd*, Paris, v, 120, pp 35-42).

Cultivation of cinchona in Java was not at first very satisfactory. On the plateau of Pentalengan the trees and seeds first planted flourished and their future seemed assured, but when analyses were made of the yield of quinine, growth having reached the stage when bark could be obtained for examination, this yield was found to be very low (1-2 per cent) with one exception and that exception grew so badly that its yield in bark was small. In 1865 the seeds obtained by Ledger, referred to above, having been sold to the Dutch, were sent to Java and analysis made seven years later showed a much higher yield of quinine, 8 per cent or so, in place of 1-2 per cent. By taking grafts from selected trees and planting them out in special gardens a further improvement of yield was obtained. After twenty years of what was really a failure financially the discovery of the Ledger variety of cinchona led to wide cultivation and success, so much so that Ceylon gave up cultivation and the Dutch Indies to all intents and purposes obtained a monopoly. As a result the quinine manufacturers amalgamated and practically dictated the price of bark, keeping a wide margin between this and their price for quinine. Then the planters organized and in 1913, after a long fight, an agreement was made providing a basis of co-operation between producers and manufacturers. In 1933 the world's production of bark was 11,666,000 kilogrammes, of which 10,000,000 came from the Dutch East Indies. The climate and the rich loam of Java, of volcanic origin, are very favourable for growing cinchona.

It was largely due to the efforts of Lady Canning, wife of the Viceroy of the time, that cultivation was started in India. During the Indian Mutiny in 1857 malaria took a heavy toll in sickness

and death, and Sir Clements Markham was entrusted with the task of procuring supplies of cinchona trees and having them planted in India. The first experiments were made in Bengal, but were not a success, the trees grew well, however, in the Nilgiri Hills of Southern India. In this country *C. officinalis* and *C. succirubra* grew best, later, *C. ledgeriana* was introduced and *C. robusta* is a hybrid of all three.

The fact that all barks were not equal in efficacy, in other words that the yield in quinine was variable, is noted by Blane in 1782 (see also p 230, above). He reported that he sometimes found Peruvian bark disappointing in the treatment of intermittent fevers and thought that in his day it was not of so good a quality as that which was used by the earlier physicians who first introduced it. A certain species, the Red Peruvian Bark, "lately discovered or perhaps revived," he found to be of a superior quality and effective in curing intermittents when the 'commoner sort' had failed. The red bark was brought to England in a Spanish prize vessel in 1781 and a very accurate account of its chemical constituents and medicinal properties by Dr William Saunders of Guy's Hospital was published in 1783.

To-day most is produced in Java and India, it has almost disappeared (says Professor Golse) in its country of origin. *C. ledgeriana* is difficult to grow, needing special soil conditions, *C. succirubra* and *C. robusta* are more hardy.

There has, almost from its first introduction, been a dispute concerning the giving of quinine, the dosage, the intervals between doses, the time relative to the fever, whether it should be given alone or with other drugs and so forth. The question can hardly be regarded as really settled even to-day. Thus, to go no further back than the middle of the eighteenth century, we find Sir James Randal Martin stating that bark may be harmful if used before the body is prepared for it "by previous bleeding, purging, vomiting and the use of attenuants," nevertheless it is necessary for the cure of severe malarial fever, but it must be properly applied. To this end he discusses its mode of action, or, rather, how it does *not* act. It does not act, he says, directly on the marsh poison, nor on the general state of the organs, nor on the blood, but has a special action on the nervous system [perhaps it was from this that Trousscau got his idea that the paroxysms of malaria were of nervous origin], it does not act by sustaining or by increasing the vital forces, nor by a tonic, astringent or stimulant action, but by a sedative stupefiant action on the marsh

poison There is no known relation traceable between its physiological effects and its therapeutic influence any more than in the administration of arsenic for lepra Large doses, he continues, are inadvisable and may be followed by blindness, deafness and insanity, therefore only such doses should be given as will cure the disease and no more

It seems to have been as common a practice in his time as it is among medical men in the tropics to-day, to give quinine in all cases of fever until the disease is proved not to be malaria, and to give nothing else Martin's conviction was that "bark will not succeed if used exclusively" He speaks of twenty-six authorities between 1751 and 1835 who all place quinine late and never first in the list of remedies for malaria Most, as one might expect, place bleeding first, then purgatives or emetics and antimonials all before bark Among them are the following Bogue, Huxham, James Lind, Sir John Pringle, Balfour, Robert Jackson, Colin Chisholm, Gilbert Blane, Lemprière, Sir James McGrigor, William Fergusson, Bancroft, James Johnson, Sir William Burnett, Sir George Balingall, Sir James Annesley, and others Of these Huxham was the physician of multiple prescription, it is stated that it was not uncommon for a prescription of his to contain a hundred ingredients and one was of 400 Chisholm does not mention bark but is a keen upholder of mercury to a point producing salivation, Burnett is another who does not mention bark but relies on bleeding and purgation

Martin advises it to be given "when the remissions are becoming sufficiently well marked," then 5-8 grains every two or three hours, but not more than four or six times, *i.e.* a maximum of 48 grains He is averse to bleeding if the patient is emaciated or worn out

Martin gives the following Army statistics of the prevalence and fatality of malaria in his day, over a number of years in different parts of the globe

Period of Observation	Place	Strength	No attacked	No dying	Proportion of deaths to admissions
20 years	Jamaica	51,567	38,393	5114	1 to 7½
18 "	W Africa	1843	1601	739	1 " 2
19 "	Mauritius	30,515	6	1	1 " 6
20 "	Ceylon	42,978	4643	868	1 " 5½
5 "	Madras	31,627	1139	54	1 " 21
5 "	Bengal	38,136	1311	89	1 " 15
5 "	Bombay	17,612	2854	114	1 " 25

His powers of clinical observation are exemplified in his statement that the influence, real or supposed, of splenic disease in keeping up the morbid train of actions of the original fever and in producing relapses is a subject well deserving the careful attention of the tropical practitioner. Now, of course, we would say that the continued enlargement of the spleen implies that the malaria has not been eradicated. M. Pierry made some shrewd deductions when he stated

- (i) That reduction in the size of the spleen bears some proportion to the quantity of the medicine [quinine] taken
- (ii) The effect produced by quinine upon intermittent fevers is proportioned to the reduction of the spleen
- (iii) The fever is cured simultaneously with the cure of the splenic disease
- (iv) On the other hand, the fever will be liable to recur so long as the spleen exceeds its proper size

Reverting to the question of preparation for quinine, Martin's method was to give emetics in the cold stage, calomel and James's powder (antimony) in the hot stage, and "bark after depletions." His custom was to give it in solution with dilute sulphuric acid. Contrary to Chisholm, he is against preliminary blood-letting. If bleeding was performed before reaction set in, *i.e.* before the hot stage, a loss of 3-4 ozs. caused prolonged and profound syncope, yet within four hours, when the reaction had come on, "50 ozs. were abstracted before any effect was produced upon the pulse, and before the sun of the same day had gone down, forty more were abstracted at one time, in all 94 ozs. within twelve hours." He is quoting a case of a Dr. Copland.

In the seventeenth century the Jesuit priests used to give in bark the equivalent of 12 grains of cinchona alkaloid just before the chill was expected, this would be about 8 grammes of the bark. Sydenham (1624-89) used to prescribe four times this amount, *i.e.* 48 grains of alkaloid, in 2 lb. of red wine, and divided this into twelve doses, giving one every four hours starting from the time of subsidence of a paroxysm. According to the type of the fever he repeated this, if necessary, in eight to fourteen days. Trousseau followed the same plan and said he preferred it to the Jesuits' method and found the powder of cinchona in Sydenham's doses far superior to the sulphate of quinine (compare the modern totaquina). If it could not be taken by mouth the rectal route is recommended by Trousseau, but he advises smaller doses "because absorption is better and more rapid than in the stomach." He also suggests quinine *endermically*, by means of

large abdominal poultices with wine and powdered cinchona kept applied for 8-10 hours Lambert's method was to apply the quinine to the skin after removal of the epidermis (presumably after blistering), the sulphate was used, not the crude cinchona which was found to act as a caustic and cause sloughing and ulceration

The use of quinine prophylactically dates from a century ago Bryson relates that of the complement of a vessel, the *North Star*, twenty men and one officer were employed on local duties at Sierra Leone and all the men took wine and bark The officer did not and he was the only one to suffer from an attack of fever Again, in 1844, two boats from the *Hydra* were detached to examine the Sherboro River, all the men were supplied with bark and wine and not one was taken ill, while the whole of the ship's crew, except the captain, who were similarly exposed for two days only without being supplied with either, contracted fever of a dangerous character

There is nothing to be gained by recording the varying opinions since that time concerning the value of quinine prophylaxis They still vary Some maintain that by taking it daily they never suffered from an attack though they lived in a highly malarious district, while all who did not take it fell victims Du Chaillu in his work on *Explorations and Adventures in Equatorial Africa*, published in 1861, has a good deal to say on the subject of malaria and its treatment, and though he obviously had a certain amount of faith in the efficacy of regular quinine, even in health, his own experience does little to support it From the time of his first arriving on the coast he took 3-4 grains of quinine every morning, nevertheless he had fifty attacks in four years As soon as premonitory signs—languor, headache, aching of limbs—appeared he increased the dose to 8-10 grains He would take this daily for a month, then every two days for a month, and afterwards during his whole stay in the country "from time to time," even when in perfect health He said that when the system became accustomed to quinine it ceased to have effect, but he found that a small dose of Fowler's solution was very successful in stopping the chills He clearly is at variance with Martin as regards dosage, for he says that between the attacks quinine should be taken in as large doses as the system can bear, "for Africa is not a place for small doses" He took it internally or by inunction, but more is needed if so taken "for the pores do not imbibe it readily," or by injection [I think he means by enema] Malignant forms of fever may kill in 24-36 hours, and Du Chaillu says that if he were

suffering from a severe attack he would not hesitate to take 150 grains in one day. If the fever returns it does so with renewed force and "the third attack is commonly fatal, the urine becomes dark red or black, the pulse irregular, breathing slow and the patient sinks into coma and dies." It would look as if he had tried these large doses on chronic cases and had been faced with blackwater fever.

The modern view is that quinine, since it has no effect on sporozoites inoculated into the blood—we have learned much about malaria since its introduction therapeutically—probably does not act as a direct parasiticide, but indirectly in some way. It has only a slight action on the sexual stage. It has been found effectual when given regularly to Europeans on estates, but not when given in tablets to coolie labourers. Perhaps the quinine in tablet form was not swallowed by the coolies, or was not absorbed, but it is probable, almost certain, that the infection among the coolies would be much more intense. In South Africa native herbalists sell quinine and most natives take it. [These South African herbalists are enterprising people. One of them pointed out to his native customers that the Government supplies of white tablets were undoubtedly suited to white people because they had white skins, those which he was selling had a central black spot without which the tablets were useless for natives. He had, it was found, gone to the trouble of boring a hole in each, and filling the cavity with a mixture of soot and fat.]

There is always the danger that the taking of quinine may engender a false sense of security and so lead to neglect of other protective measures. There is abundant evidence that quinine is an inadequate prophylactic alone. We have already mentioned Wenyon's report that, in Macedonia in the Great War there were thousands of instances where infection showed itself in men taking quinine regularly, on the other hand the brothers Sergeant reported how the danger of malaria in the French Army in Macedonia was overcome by the proper use of quinine, this being proved by testing the urine with Tanret's reagent. If the results were not satisfactory the officer, not the private soldier, was punished. It is recorded that in September 1916 there were 8000 primary cases in four divisions, in 1917, with eight divisions, primary cases were less than a thousand. In 1916 there were 379 deaths from malaria, 71 in 1917, and 54 in 1918. Tanret's test showed that less than 2 per cent of the men were taking the quinine in 1916, whereas in 1918 nearly 100 per cent did so.

Robert Koch, from observations made in Java and Sumatra,

concluded that quininization of the people was a very judicious measure and that the diminution of cases in the Dutch Indies was due to it. Others object to the term 'prevention of malaria' by quinine, for the alkaloids of cinchona do not prevent the disease, they merely attack the parasites when they are in a certain stage of their development. Quinine does not inhibit infection through the bites of *Anopheles*. As Yorke and Macfie have shown it may inhibit attacks of fever for a time, but these recur on cessation of taking the drug. Marchiafava and Bignami held that quinine inhibited the nutritive processes which enable the parasite to develop to the stage when they are ready to segment. No change was observed in the parasites, but it appeared to act deleteriously on the spores when they became free in the plasma, so that they were not able to invade fresh corpuscles and disappeared.

Koch's method was tried in Italy and in the French and German possessions but the results were not as good as the antimosquito measures used, e.g. in Klang and Ismailia. In Malaya in 1904-5, Sir Malcolm Watson reports, the results were good at first, but, many non-immune labourers coming in in 1906, the dose had to be increased and even then was not effectual. It acts by assisting the human host, increasing his resisting power or attenuating the virus.

Without quinine in many cases, especially in very unhealthy spots, the human host would die before he had acquired his resistant powers.

If quinine in sufficient doses be given the man will gradually overcome the parasites and apparently suffer little from them, but at the same time during this period he is capable of infecting others.

Quite recently (1937) S. P. James and P. Tate have shown how it may come about that banishing the plasmodium from the blood-stream does not cure a person infected with malaria. They worked with the newly discovered *Plasmodium gallinaceum* of fowls and showed that a cycle of development took place, not in the red corpuscles, but in the reticulo-endothelial cells of the spleen, the liver, kidneys and the capillaries of the brain. They found that even when quinine had destroyed all the parasites in the peripheral blood the capillaries of the brain were blocked with masses of schizonts and death occurred from paralysis and coma—in other words, there is a schizogenous cycle of development in the reticulo-endothelial cells. The parasite enters the blood-forming cells and multiplies until the merozoites burst the cell, enter other endothelial cells and red corpuscles and start the cycle afresh. This may not, of course, apply in man, but we should

remember that Ross's work was first shown in birds and also MacCallum's observation of impregnation of the macrogamete by the flagellum. The inference from this is that, since the drug circulating in the blood-stream cannot attack extra-hæmic parasites, there is no short cut to treatment, that, though plasmodia in the blood have been destroyed, the parasite can maintain itself elsewhere, in the reticulo-endothelial cells, and consequently a patient taking quinine regularly while in a malarious district and for the duration of the incubation period of malaria after leaving that district, may still suffer from an attack later. Hence, as is by no means infrequently observed, a person leaving the West Coast of Africa, for example, having religiously taken his daily dose while there and for 10-12 days after leaving it, and then stopping it feeling that he has eradicated the plasmodium and is free from danger, on arrival in the cooler weather at home suffers from an attack, sometimes very severe, perhaps takes a large dose of quinine and falls a victim to blackwater fever.

One more striking instance may be given of the failure of quinine alone as a prophylactic. It was relied upon to prevent disease on some estates in Southern Indo-China, but malaria increased to such an extent that the land was abandoned. In others the loss, terrible at first, became gradually less and after a few years, in spite of the fact that no other steps had been taken, the estates seemed to effect their own deliverance. Although the sick rate was only 3 to 10 per mille, the splenic index was 84 per cent and the parasitic index not far below it. The improvement was ascribable, therefore, to what is known as 'premunion' or acquired tolerance associated with latent infection. Non-immune children suffered severely, the birth-rate was low, abortion and infant mortality rates high. It took about five years to reach this state of equilibrium of a kind, provided no fresh labour was imported, new non-immune arrivals meant a fresh malaria outbreak. In their earlier years these estates had disastrous returns. For example, in one plantation out of a labour force of 650 coolies, 200 died in the first year, antilarval work *plus* quinine reduced the daily sick to 2 per cent in a year, although prophylactic quinine alone had not lowered the infection rate.

Before mentioning, as of historical importance, the modern developments of malaria therapy, reference may be made here incidentally to other plants reported to be useful in treatment of this disease. Livingstone mentions a plant used by the Portuguese at Tete, Senna, and Kilimane delta, in place of cinchona. In fact the Portuguese thought it was cinchona and informed

Livingstone that they had forests of it and regarded it as providential that the remedy for fever should be found in such abundance where it was most needed. Livingstone sent parts of the tree—leaves and seed-vessels, he tried to transport some small living trees, but they died—to Dr Hooker who declared it to be “an Apocynous plant very nearly allied to *Malouetia Heudlotii* (of Decaisne), a native of Senegambia.” Various plants of this order were said to equal cinchona in their febrifuge effects. The native name for this species was Kumbanzo. Livingstone having come to the end of his supply of quinine, made a decoction of the ‘bark of the root’ and it proved very efficacious, given after the first paroxysm of the fever was over. His men collected it and kept it in bags for future use. Other plants used by the natives for these fevers were *mupanda panda*, the leaves named *chirussa*, *kapande* which in large doses is used as an ‘ordeal’ plant, *Itaka*, brought to Kilimane for barter by the Arabs and eagerly purchased by the natives, and *mukundu kundu*, a decoction of which was used like quinine, it grew abundantly at Shupanga. Unfortunately, with exception of the first no details are given by which their genera or species can be traced. It might be worth while investigating some of these native plants used as febrifuges in intermittent fevers.

Hymenodictyon excelsum velutinum is a tree closely allied to the cinchona. It was discovered by Balsana in Indo-China in 1881. After his death no mention is found of it until Joyeux, Guichard and Poilane rediscovered it in Tonking in 1936. They found it growing abundantly near the frontier of Annam and Laos in the valleys and at low altitudes. Its bark is said to contain ‘neither quinine nor any other alkaloid’. Observations are being made as to its efficacy, but no reports have yet been issued.

In 1928 a subcommittee of the Medical Research Council undertook an inquiry into the relative efficiency of the different alkaloids of cinchona bark. They came to the conclusion that quinidine is as powerful as quinine in the immediate cure of the disease and that cinchonine and cinchonidine possess about 75 per cent of its strength in this respect. On these grounds the use of the total alkaloids has been recommended in order that a more plentiful and less costly remedy than quinine may be available.

This leads us to say a few more words on *totaquina*, a mixture of alkaloids, 70 per cent crystallizable alkaloids and not less than one-fifth quinine (see above, and Martindale’s *Extra Pharmacopœia*). It is, thus, a standardized cinchona febrifuge. There are two types—one made direct from the bark of *C. succirubra*

and the other from residues of quinine extraction. Trials were carried out, under the auspices of the Health Organization of the League of Nations, at Kuala Lumpur, Nanking and elsewhere, and they showed that totaquina is valuable in all forms of malaria. The result of trials with it on prisoners in Lahore, in tertian and subtertian infections, showed that both forms of the preparation were as efficacious as quinine and neither seemed to be the more toxic. They have no action on subtertian gametocytes.

Other drugs containing quinine which may be mentioned are esanofele which contains also iron, arsenic and bitter herbs, and tebetren which combines acridine and quinine derivatives with a derivative of cholic acid. It has good effects as regards the malaria, but its side-effects—deafness and tinnitus—reduce its usefulness.

Arsenic is an old remedy in malaria, not as a substitute for cinchona or quinine, but as an adjuvant. It was so used by Du Charllu, as already stated, and it formed the essence of Dr. Boudin's treatment, a century or so ago, who himself says that it is not to be given in place of cinchona, but as a

complex medication in which arsenic sets up an arsenical in opposition to the paludal diathesis, seconded by emetics to combat gastric disturbance [*sic*] and accelerate restoration of appetite and alimentation to shorten the period of convalescence.

He therefore starts with ipecacuanha and follows it by arsenious acid, $\frac{1}{2}$ –1 mgm. for eight days for the first invasion, but the duration of administration must be proportionate to the length of time the disease has existed, fifty days or even more.

In recent times arsenic has been used in the form of stovarsol. This is 3-acetylamino-4-hydroxyphenylarsonic acid, with the formula $\text{CH}_3\text{CONH C}_6\text{H}_3(\text{OH})\text{AsO}(\text{OH})_2$, and has other names such as acetarsol, kharophen, orarsan and spirocid. It is used more in French than British colonies and has been found beneficial in chronic and cachectic cases. It acts only on the benign tertian parasite and does not prevent relapses and is consequently more often used in combination with quinine, as quinio-stovarsol. Another closely similar preparation is quinine troposan, containing 50 per cent quinine and 40 per cent troposan (11 per cent arsenic) which is an isomer of stovarsol.

The list of drugs and nostrums which have been recommended and tried in malaria is a long one, enumeration of some of them may be of interest, but with two or three exceptions mere enumeration will suffice. Zinc sulphate, Warburg's Tincture, Albert 102, dimeplasmin, A-malarin (glucoside of dioxidiaminodiphenyldi-

arsenide, of doubtful if of any benefit), antimosan (5 per cent solution of Heyden 661 which itself contains 12.5 per cent tri-valent antimony), colloidal sulphide of antimony (of some good in benign tertian), aseplene (composition unknown, a proprietary preparation found valueless in trials at Kuala Lumpur), berberine, cadmium, diémenal (colloidal manganese, perhaps should be given further trial), elevosan, mercurochrome 220, with the formula $C_{20}H_7O_5Br_2HgOHNa_2$, plasmogune, atebirin, *Læselina cucinea*, *Calliandra grandiflora* (from the Argentine, has no effect on the disease), paludismol (contains extracts of *Senecio salignus*), peracrina 303, rhodoquine U (Fournéau 915), sinomenine hydrochloride (from *Sinomenium diversifolium*, good results recorded, it cleared the blood of parasites in two to nine days and there was no recurrence for seven months. Only twelve cases were, however, reported and a further trial is called for), smalarina.

Blane is the only reference we have been able to find extolling the use of white vitriol or zinc sulphate. With it, he says, he obtained success in intermittent fevers when bark failed. He gave 5 grains every four hours during the intermission. He maintains that it is not to be compared generally with bark, nor as a substitute in all circumstances, but is a valuable subsidiary in particular cases. He was wise in his generation, for he adds that he does not like to praise it too highly because

many good medicines have had their characters hurt by being over-rated by the first proposers of them, who are naturally sanguine and partial, without, perhaps, intending to deceive. But when others find that their virtues do not come up to what has been asserted, they are apt to run into the other extreme and explode them altogether, so that what was given out as good for everything is now found to be good for nothing.

Warburg's Tincture, *Tinctura antiperiodica*, cannot be passed over, since for many years it had a great vogue and few ventured abroad without it. There can be no doubt that so favourite a preparation and one which retained its reputation for so many years must have done good, though to which of its ingredients the benefit is to be attributed is somewhat a matter of guesswork. Its constitution was as follows

Socotrine aloes	1 lb
Rad rhœi (Chinese)	
Sem angelicæ	
Conf Damocratis	4 ozs of each
Rad helern (S enulæ)	
Crocî sativi	
Sem fœniculi	

Cretæ precipit	2 ozs	of each
Rad genitanæ		
Rad zedorariæ		
Pip cubebæ		
Myrrhæ elect		
Camphoræ		
Bolet larisis	1 oz	„ „

These fourteen constituents were digested with 500 ozs of proof spirit in a water-bath for twelve hours, then expressed and to the residue were added 10 ozs of sulphate of quinine and the whole placed in a water-bath again until the quinine was dissolved and the product filtered after cooling

By some it is said to contain also opium (0.03 per cent), the dose was 1-4 drachms. The whole must have been a formidable prescription to prepare though it pales before those of Huxham who, as already mentioned, gave prescriptions with a hundred or more ingredients

Coming down to post-war times there remain plasmoquine (and plasmoquine compound) and atabrin which demand a few words. Mueh, in fact hundreds of papers, has been written on these, but William Fletcher's article (*Trop Dis Bull*, 1933, v, 30, p. 193 *et seq*) gives an excellent summary from which the gist of what follows is taken. Experiments were carried out at Elberfeld with a view to finding a synthetic drug which would take its place when the supply of quinine fell short, as it did during the War. The investigation was narrowed down to the arsenicals and methylene blue, and among a large number of preparations of the latter one was found particularly active on *Plasmodium relictum* in canaries, which were the experimental animals. This one was at first called beprochin and afterwards plasmoquine, and proved better even than quinine in avian malaria and tests were made on man. It has the formula $C_{15}H_{25}ON_3$, whereas that of quinine is $C_{20}H_{24}O_2N_2$. It proved capable of destroying all forms, schizonts and gametocytes, of benign tertian and quartan malaria and the sexual forms of subtertian, but was ineffectual in the treatment of malignant tertian fever because it did not affect the schizonts of *P. falciparum*. For such infections, therefore, it was combined with quinine—plasmoquine compound. It has the additional advantage of being a true prophylactic, but the dose required is too large for absolute safety. At first the doses given were too large and toxic symptoms occurred, often with alarming suddenness—abdominal pain, cyanosis, lividity of the lips, passage of black-coloured urine.

Further study at Elberfeld of more than 12,000 compounds

led to the production of *Erion* or *Plasmoquine E*, a body now known as *Atebrin*, with the composition Dihydrochloride of 2-methoxy-6-chloro-9- α -diethylamino- δ -pentylamino-acridine. Its action on the malaria parasites was analogous to that of quinine, destroying all forms of benign tertian and quartan and the schizonts of subtertian, but not attacking the gametocytes of the last. Fortunately its toxicity is low and double the usual daily dose can be tolerated, larger doses cause gastric pains and the drug may stain the skin and conjunctiva yellow (not a toxic effect). It differs from quinine in remaining much longer in the body, being found in the urine in some cases four or five weeks after a seven-day course. This fact may be utilized for prophylactic purposes.

A few words in conclusion concerning a derivative of the last—atebrin dimethanesulphonate, or atebrin musonate—a preparation intended for intramuscular or intravenous injection. It cannot, however, at present be regarded as a safe drug, convulsions, collapse and death have followed its use, others exhibit as toxic symptoms rapid respiration, vomiting, collapse, abdominal pain, headache and diarrhoea, yellowness of the skin and peculiar psychoses. In others again the results were good, the schizonts rapidly disappearing from the blood. It is excreted slowly and as it is, at present, not possible for us to say beforehand which patients may take it well and which may react badly, and moreover, as it is difficult to hasten its excretion, it is perhaps wiser to await further experimental work before it is adopted into the regular armamentarium of the tropical practitioner.

Premaline is a new synthetic product similar in action to a combination of quinacrine and rhodoquine in attacking both schizonts and gametes. It has been tried in Saut-Vata, an intensely malarious place in French Guiana, especially from November to March. Fifty men were stationed there. In the beginning of September, 1936, their parasitic index was 29.6 per cent. From 7th September to 15th December three tablets of premaline were given once a week, from 15th December to March three tablets twice a month. No other antimalarial measures were in force. Fifteen days after starting the treatment the parasitic index was nil and remained so until the end of February. In a neighbouring post, used as a control, malaria was as intense as usual and fatal cases occurred.

9 RECENT DEVELOPMENTS AND CONCLUDING REMARKS

Since 1916 the International Health Division of the Rockefeller Foundation has assisted various countries in antimalaria schemes

working hand in hand with their respective governments, notably in the Argentine, Porto Rico, Nicaragua and Brazil, in addition, of course, to the United States. In 1924-5 a similar helping hand was held out to Italy, Poland, Palestine and the Philippines.

An even more promising scheme, more promising because it envisaged the pooling of international knowledge and of the researches of malariologists all over the world, had its origin in England in 1923, when various European countries were trying to arrange a continuous health policy. In May that year a proposal was put before the Health Committee of the League of Nations and as a result of its deliberations a Malaria Sub-Committee was first appointed and later a Malaria Commission to collect information from the United States, British India, Sicily, Spain, Palestine, Rumania and other countries. The results were discussed in full session by malariologists of repute belonging to different schools and having different opinions and the views of men of various ways of thought were brought to bear on local problems. The good that has resulted and is likely to accrue in the future from such a procedure is inestimable.

Another body of workers whose accomplishments must not be passed over in silence is the official central organization, the Malaria Survey of India inaugurated by the Central Government a few years after the War. Its primary object was to conduct research into the question, in any or all of its branches, to serve as a bureau of information and advice, to issue bulletins, to aid those engaged in malaria research and prevention, to train medical men in laboratory and field technique, to identify specimens forwarded to them and to undertake special investigations directed to setting up methods of control. The records are published from time to time and are invaluable to all malariologists.

Passing from the general to the particular, of special historical interest is therapeutic malaria, that is, the deliberate inoculation of a patient, suffering from some other disease, with malaria for purposes of treatment, amelioration or cure. We have learned a good deal about malaria by this means, for we have been able to test under experimental conditions certain points formerly in dispute. The knowledge, however, is limited by the fact that the work has practically all been done in temperate climates and that the use is restricted to benign tertian parasites—*P. vivax* or *P. ovale* being the only ones employable with safety.

Though its application, at all events on a wide scale, is of comparatively recent date, the idea was mooted or adumbrated

a century and a half ago, when Korowitz in 1775 reported that a woman with cancer of the breast contracted a double tertian fever and that the tumour gradually disappeared. It was on the basis of this record that Löffler in 1901 suggested that cancer patients might be treated by a mild form of malaria, adding that amongst tropical natives in whom malaria is ever present cancer seems to be very rare—of course, a type of reasoning obviously fallacious, though on all fours with the prevailing notion that neurosyphilis, general paralysis and tabes dorsalis, is uncommon in the tropics on account of the prevalence of malaria.

Prior to Löffler a Viennese physician, Julius Wagner von Jauregg, in 1887 had observed that febrile disease might influence favourably psychoses and nervous conditions, and in particular pareses, and he made further study of the subject in the ensuing thirty years. In 1917 he began to treat soldiers suffering from paresis by means of inoculation of malaria. Two years later Plaut reported that a like benefit followed fever produced by other means, for example *Spirochæta recurrentis*. At first the blood of malaria subjects was used, later the safer method of allowing infected mosquitoes to bite the patient was substituted.

Malaria therapy, that is the treatment of disease by deliberate infection with malaria, has opened up a wide field of research—clinical and epidemiological as well as therapeutic—on human malaria contracted as in nature. In May 1925, a malaria research laboratory was established at the Horton Mental Hospital, Epsom; reports on the work done there were issued from 1926 onwards, and other laboratories on the same model were soon established in Italy, Holland, Rumania and the United States.

The latest report on the *Provision and Distribution of Infective Material for the Practice of Malaria-Therapy in England and Wales* (No. 84 of *Reports on Public Health and Medical Subjects*) written by Lieut-Colonel Sinton and published in July 1938 gives an account of the development and progress of the undertaking. In this we are told that at the 'mosquito farm' 27,000 mosquitoes have been bred from a single female and infected with malaria ready for therapeutic application. The most recent reports of the results of this form of treatment show that 49.1 per cent of patients were favourably influenced and 24.8 per cent were discharged 'cured' or 'improved'. In the first eight years from 1917 the demands for mosquitoes became so numerous that, as stated above, the Horton unit was established consisting of mosquito-proof wards holding twelve beds and two small rooms fitted up for laboratory work. This accommodation has since been extended

to the erection of special wards for twenty-three patients, and even this is becoming insufficient

The method adopted is to apply laboratory-bred mosquitoes in batches in jars to the thigh of a selected malaria patient. After feeding, the insects are removed to a special 'hot room' and kept there till they become infective. When required 15-20 of these are taken in a jar, packed in a leather case to prevent breakage of it and consequent escape of the insects, to the patient and are allowed to bite him on the thigh through gauze covering the mouth of the jar. To ensure infection at least ten mosquitoes are allowed to bite.

Another recent development which must be mentioned because the literature concerning it has already reached alarming proportions is Henry's method of diagnosis. This was first brought to notice in 1927 in a paper entitled *Contribution à l'étude sérologique de l'infection palustre*, read by A. F. X. Henry at the Fifty-first Congress for the Advancement of Science held in Bordeaux. The principle, which is all that is of historical interest, was that the serum of malaria patients produced a flocculation when mixed with a 1-per-cent solution of methyl arsenate of iron (metharfer). The following year he showed that melanin from the choroid and vitreous of bullock's eyes, with addition of formalin and distilled water gave a similar flocculation and also deviation of complement with malaria serum. The test seems to be based on the presence of two kinds of pigment derived from hæmoglobin, a yellowish ferruginous pigment and melanin, and it was thought that these might produce antibodies in the blood. The albuminate of iron is now used for the first, methyl arsenate. There is still some dispute as to its value in diagnosis, some are in its favour, others believe that the flocculation is due to dilution of the serum-globulin and that the precipitate is coloured by the melanin.

While on the subject of diagnosis we may also refer to the adrenalin method proposed in 1919 for diagnosis of latent malaria and now become the basis of what is generally known as Ascoli's method of treatment of chronic malaria. The injection of adrenalin by setting up splenic contraction drives the contents into the circulation and within twenty minutes malaria parasites appear which before could not be seen in smears of the peripheral blood even after prolonged search. The numbers usually increase to reach a maximum about an hour after the injection.

In a work treating of the history of malaria the discussions which have of late years taken place relative to the question of congenital malaria and of immunity to malaria infection should

receive passing mention. Professors D B Blacklock and R M Gordon, in Freetown, Sierra Leone, examined the placentas of 150 parturient women suffering from malaria and in fifty-five found the parasites, *P falciparum*, although many showed none on their peripheral blood being examined. Examination of the children's blood and of the umbilical cords revealed no parasites, they were present in the maternal part only of the placenta. Schwetz, in Central Africa, on the whole confirmed this, though parasites were present in the peripheral blood of mothers and were still more numerous in the placental blood, he was unable to find them in the blood of the new-born infants. But in another series he found two children congenitally infected out of fifty-six. Van Nitzen recorded four cases in 1934 in the *Bull Méd du Katanga*, the parasites were present in the infants' blood, in one on the second, one on the third, and two on the tenth days. Amando Barbosa and Benito Lopez Arjona produced in 1935 an excellent paper with a report of their investigations. Their paper was entitled *El paludismo en el primer año de la Vida*, and was published in Cáceres. They show that congenital malaria undoubtedly does exist, but the number of cases is very small. The disease leads to abortion, premature birth, dead birth, and birth of infants with enfeebled constitutions, so that they are liable to succumb to what would be a mild infection to a healthy child. Much of these might be due to fever bringing about uterine contraction, or to anæmia of the mother, to toxins initiating contractions, and so forth.

Passing to the second question, immunity to malaria. There are rare cases in which persons live for years in tropical countries, take no special precautions, do not take quinine and yet do not suffer from malaria. The general rule is a gradual development of a partial immunity only. Thus, for example, Christophers investigated a labour force in a hyperendemic area in Chota Nagpur in 1924. Among the children the spleen rate was 70 per cent, among the adults only 10 per cent. Christophers and Stephens found in Lagos every child under two years became infected, but from two to five years only 71 4 per cent. In Sierra Leone it was noted that natives were less irritated by mosquito bites than were Europeans, but they attracted more mosquitoes; so in a tent with Europeans there were only a few, whereas they swarmed in the native tents and when the natives left the mosquitoes were fewer.

Further study convinced Christophers that acute infection occurred in early life—the first two years—the blood containing

about 10,000 parasites per cubic millimetre, then followed an 'immune infestation period' with a reduced parasite rate lasting to adult life, attacks occurring every two to four weeks in childhood, every six months or so in adult life. Examination of adults showed that only about half of them had demonstrable parasites in their blood and those in small numbers, 100 per cmm, the others having developed an immunity.

Children coming to the district of hyperendemicity at a later age, over five years, went through a milder period of 'acute infestation,' showed larger spleens in the period of 'immune infestation.' The acquired immunity is evidenced by the individual being able to live free from sickness, though infected, whereas the newcomer and the new-born suffer almost continuously from heavy infection.

Apart from the differentiation of species of parasites—*vivax*, *ovale*, *malariae*, *falciparum*—there is the question whether there are not different strains of the same species, as occurs, of course, in bacteria. Thus, it is well known that Indians may be exposed for many years, even throughout life, to malaria in their own country, and would in consequence be expected to have established or acquired a certain tolerance, if not immunity to infection by, say, the subtertian parasite. Nevertheless, on coming to a new country—an Indian coolie imported to Jamaica, for example—they may suffer severely from malaria due to the same species of parasite as that which had attacked them and in contact with which they had lived for the whole of their life till then, and had not perhaps for years shown any signs of susceptibility or any serious attacks of fever.

SUMMARY OF IMPORTANT DATES IN THE HISTORY OF MALARIA DISCOVERY

- 1640 Introduction of cinchona
- 1717 Italians employed drainage as a preventive measure against agues
- 1753 The name 'malaria' given to the disease by Torti [?]
- 1793 First account of the use of oil for destroying mosquito larvæ
- 1847 Meckel recognized characteristic pigment in the blood, spleen, liver and tissues generally of persons dead of malaria
- 1848 Virchow recognized the pigment in cells resembling leucocytes and Frerichs saw refractile granules in the contents of the small blood-vessels of the brain
- 1854 Planer demonstrated the presence of pigment in the finger-blood of a patient
- 1875 Kelsh saw granules of pigment in the blood corpuscles of malaria patients and in

- 1880 Concluded that these granules were diagnostic
- 1880 23rd November, Laveran made known his discovery of amoeboid, crescentic and flagellating forms of parasite
- 1881 Mosquito nets first used in India [?]
- 1883 Marchiafava stained dried blood films and observed the ring forms. He affirmed that these were the parasites and that the bodies described by Laveran were not the genuine thing. Italians till now had clung firmly to Klebs and Crudeh's 'bacillus of malaria'
- 1883 Publication of King's paper in America giving his reasons for believing that malaria was transmitted by mosquitoes. There had been vague belief before this, but King's was the first reasoned justification
- 1885 Marchiafava and Celli produced the disease by inoculating human beings with blood containing the parasites
- 1885 Golgi described the development of the quartan parasite and separated the tertian and quartan by the periods of their respective development, and noted that the rise of the patient's temperature coincided with liberation of the spores
- 1889-90 Marchiafava and Celli differentiated tertian and quartan (spring) forms from the malignant æstivo-autumnal form
- 1893 Bignami and Bastianelli determined the incubation period of æstivo-autumnal fever by inoculation of blood containing the parasites and showed that fever did not follow if blood containing crescents only were injected
- Incidentally, this year Smith and Kilborne were the first to show, in piroplasmiasis of cattle, that the bite of an arthropod could transmit disease
- 1894 Manson put forward the 'mosquito-malaria theory'. Suggested that flagellating bodies were set free in the stomach of a mosquito and that these gained access to water through the insects drowning in it and that man acquired infection by imbibition of the water
- 1895 Ross started working at the subject in India
- 1897 MacCallum, of Johns Hopkins University, observed fertilization of halteridium in birds by penetration of microgametes (flagella) into macrogametes to become mobile vermicles, and subsequently showed that the same occurred in human malaria
- 1897 20th August. Ross found pigmented bodies (oocysts) in the stomach-wall of 'dapple-winged' mosquitoes bred from larvæ and allowed to feed on a malarious patient
- 1898 Ross, finding too few cases in Calcutta where he was working, carried on his investigations on the disease in birds and showed the course of evolution from sporocysts and that sporozoites invaded the salivary glands of *Culex*
- 1898-9 Bignami, Grassi and Bastianelli demonstrated that the same cycle occurred in *Anopheles* after feeding on human malaria patients
- Koch and Pfeiffer confirmed Ross's findings in birds as applicable to human malaria
- Foundation of the Italian Society for the Study of Malaria
- 1900 Sambon, Low and Terzi lived in mosquito-proof hut in the

Roman Campagna and showed that protection from mosquito bites protected also from malaria, in other words, with proper precautions non-immunes could live in a highly malarious district with impunity

- 1900 Manson infected his son by means of infected mosquitoes sent from Italy, proving that to a non-malarious district infection can be brought from a distance by infected mosquitoes
 Appearance of Grassi's illustrated monograph showing complete life-cycles of the parasites
- 1920 Introduction of larvicide in powder form—trioxymethylene—by Roubaud
- 1921 Hayne and Barber introduce Schweinfurt (or Paris) Green as an effective larvicide

GENERALIZED SUMMARY OF THE GEOGRAPHICAL DISTRIBUTION OF MALARIA AT THE PRESENT DAY

There are three recognized zones, namely, temperate, sub-tropical and tropical

I *Temperate* That is between 40° and 60° N Benign tertian is the prevailing form, distribution is inclined to be patchy, most of the area is free, in some places it is comparatively severe. In the corresponding zone in the Southern Hemisphere malaria is uncommon

II *Subtropical*, between the tropic of Cancer and 40° N and the tropic of Capricorn and 40° S Subtertian and benign tertian both common, the former often becoming epidemic in the autumn

III *Tropical* Subtertian is the predominating type, is almost general in distribution and its season is prolonged, near the equator it may persist throughout the year.

There are countries where all the known conditions appear to be present to foster malaria—suitable insect vectors, infected immigrants, non-immune residents, temperate and climate favourable—nevertheless the infection does not spread. The reasons for this we do not know. The disease may occur in one place and not in another apparently similar, only a mile or so distant. Perhaps there are no convenient breeding sites near the latter, and the winds are not favourable for conveyance of insects. Infection may occur in the outskirts and suburbs of large towns, but not in the centre, Rogers thinks that a potent reason for this is the construction of closed drains in the towns

Again, the climate may apparently be favourable, for example, that of New Caledonia, Madura, Barbados, Fiji, but malaria is absent, it may be because the suitable vector is wanting. Bar-

bados was attacked in 1926-7 Mauritius and Réunion were for a long time free, but in 1864 infected coolies were imported, Anopheles were already present, the non-immune population were at hand and the epidemic we have described above arose

In Denmark and elsewhere it has died out and England is almost free, agricultural developments, zoophilism, general improved hygiene are probably responsible, other factors have been mentioned in foregoing pages On the other hand Corsica is an example of a country formerly highly cultivated and healthy, now very malarious

The situation to-day [writes Wallace of Kedah, Malaya] is analogous in some respects to that which arose after the epoch-making discoveries of the mosquito cycle of malaria, nearly forty years ago Now, as then, new knowledge of fundamental importance is available, but we have yet to learn how it can be applied and utilized effectively in practical antimalarial work Many more discoveries, biological and chemical, will have to be made before it will be safe to say that the solution of the malaria problem in the world generally is appreciably nearer than of old

CHAPTER VI.

BLACKWATER FEVER

To all who are engaged in the study of tropical medicine, and particularly to those who are sufficiently interested to delve into its history, it is a subject for constant wonder that, whereas malaria has been recorded for twenty-five centuries, blackwater fever, so far as we know at present, has been observed for little more than one, and no recognizable description of it has been discovered before the latter half of the nineteenth century. The question whether the fifteen patients with black urine and three with red, whose cases are recorded by Hippocrates, were suffering from blackwater fever has been discussed again and again, but the evidence is not sufficient for a decisive statement, other symptoms than the *μέλαινα ούρα* would lead to the conclusion that they were not, and the absence of any record from Greece where the disease is now quite common, or any other country in Europe between the middle of the fifth century B C and the nineteenth A D certainly calls for explanation from those who support the view that blackwater fever was known to Hippocrates. Notable and accurate observers, such as Torti in Italy and the earlier writers on disease in India, make no mention of it, it is, therefore, at least doubtful that it existed in their day. Such absence of record is one of the reasons adduced for thinking that the disease is of recent origin and is used as an argument in favour of it being a disease *sur generis*.

A line of argument, merely a *petitio principii* often employed, is a refusal on the part of those who ascribe it to quinine to recognize other conditions as being blackwater fever at all. They maintain that Hippocrates's cases cannot have been blackwater fever as we know it because the Greeks of his time had no quinine. On the other hand, the Greek physician of recent days has certainly as good an acquaintance as, and probably better than, anyone else with the condition and many of them, of whom may be mentioned Antoniadès (1858), Cardamatis (1900), Kouzis (1908) and Alexandrides (1932) are of opinion that the condition in

Thassos in Hippocrates's day was blackwater fever Stephanos in 1884 said that it was common in Sperchios Valley (Thessaly), outbreaks having occurred in 1858-9 and 1864-6, and it is frequent there at the present time

After Hippocrates we find no reference to blackwater fever or anything which can be so interpreted for 1150 years Then there is mention of it by Theophilos Protospatharios and five centuries later Actuarius, the last of the known Byzantine writers, refers to black urine with fever and jaundice Then follows another interval, this time of seven centuries, to Antoniadès (1858) who called it *hæmaturia* (see later)

Search in the literature for records of the condition in tropical countries enables us to trace them back to 1822, but not prior to that with any certainty In Boyle's *Fevers of West Africa*, a work published in 1831, the author states that Tedlie on the Gold Coast spoke of a condition occurring in some patients attacked by the endemic fever of the Cape Coast in which the urine had "the appearance of bloody water" During the ensuing decade the disease is not referred to, but in 1832 there is note of the first death attributed to this occurring among Basle missionaries who had settled there four years earlier In the next eight years, that is by 1840, deaths from this cause had been numerous

In the meantime, in 1828, cases had been reported at Guadeloupe with symptoms which bore some resemblance to those of yellow fever, but differing from the usual type of this disease, this is clear from the name given to the malady, *fièvre jaune des acclimatés et des Créoles*, and it occurred at a time when there was no prevalence of yellow fever of the well-known type (*époque de l'immunité pour le fièvre jaune*, writes Dutroulau in 1861, and he mentions Dr L'Hermier as his authority for the disease attacking the native born)

From this time on reports of the disease came from various parts of the tropical and subtropical world, whether as a condition till then unknown, or as one of older standing which had till then escaped observation or been regarded as an atypical form of disease well known, we cannot decide

In 1830 a case occurred in St Lucia, as reported by Evans in 1837, records prior to that date are not conclusive We hear of cases in the United States, Illinois and Indiana, also in 1837, and possibly there are records of it earlier, it is generally known as occurring in several States a few years later In 1842 Mavroyannis recorded it in Greece and in 1848, as noted already, saw it

at Nauplia In the 'fifties come records from Madagascar, Lebeau in 1851 and Le Roy de Méricourt in 1853 announce its being seen there and in the near-by island of Nosse Bé Its presence in Nicaragua is reported by Mense to have been observed in 1850, many cases among foreigners, a few among the indigenous population, in 1851 cases were observed in Senegal and became frequent enough for the disease to be mentioned in the hospital statistics of Gorée and St Louis four years later Within the same decade more cases were reported in Greece, in 1858 by Varetas who noticed its occurrence after administration of quinine, and he and Antoniadès, and probably others, noting 'hæmaturia' as a not infrequent symptom of intermittent fever following administration of quinine, connected the two and some of them concluded that the former was the result of poisoning by the latter Nevertheless, Antoniadès himself was not a supporter of the quinine intoxication hypothesis, in fact he regarded "the withholding of quinine in cases of hæmaturia [*i.e.* hæmoglobinuria] as criminal negligence", and we may note here that most cases of blackwater fever in Greece to-day are treated with gramme doses of quinine Varetas the following year expressed a different opinion and believed that quinine when given to patients suffering with intermittent fever provoked hæmaturia, though some were more sensitive to its action than others Antoniadès reiterated his views two years later in a paper with illustrative cases In 1861 Paravassiliou brought forward evidence supporting Varetas and in 1872 Rhizopoulos recorded several cases, some in whom the condition arose after the patients had taken quinine, others to whom quinine had not been given and some whom he treated by giving quinine

Six years later (1878) Karamitsas wrote on *Hæmaturia or Hæmoglobinuria from Quinine*, stating that the urine contained not blood but hæmoglobin Writing in *Niemeyer's Medical Pathology* he hedges a little.

In some patients who have intermittent fever quinine provokes hæmaturia, which must be distinguished from the hæmaturia that follows it without quinine, and the urine must be examined to discover whether blood or hæmoglobin is present

From this and other statements one gathers that in his opinion there were two types—hæmoglobinuria caused by quinine and that caused by malaria—but his writings are not sufficiently definite to enable one to say whether he thought the malaria was a necessary concomitant of the quinine

In 1869 a definite instance was reported from Jamaica by

Croskery as having occurred the preceding year—a planter, 37 years of age, dying with suppression after passage of urine the colour of 'dark porter'. The same year J C Cummings of Monro, Louisiana, described six cases and mentions that several had occurred the year before. Thus we see that the decade 1850-60 was fruitful in reports of cases from the Old World and the New.

In 1863 British Guiana reported cases, and the following year we hear from Le Roy de Méricourt of others in Panama and Punta Arenas (Costa Rica). In 1866 H C Ghent of Port Sullivan, Texas, reported that hæmoglobinuric fever was endemic there and the following year R T Michel of Montgomery, Alabama, describes the condition under the designation "malignant malarial fever". It was not, it appears, till 1867 we first hear of a case in Algeria, a man of 36 years, reported by Arnould. In 1871 Du Val records the first known case in Arkansas, and in 1872 W A Greene the first in Georgia. The next record is from the East, a man of 42 years who had died with suppression after passing "bloody urine", this was reported by E A Birch in the *Indian Medical Gazette* of 1879 as having occurred the year before, in 1879 it was noted also in Nowgong, Assam.

S R Christophers (now Sir Rickard Christophers) pointed out nearly thirty years ago how gradual has been the recognition of the existence of blackwater fever, not because the condition has spread from one place to another but because its nature was unknown and unstudied. We have mentioned above in more or less chronological sequence the reporting of cases, but, as Christophers points out, the records may be grouped in a striking manner according to nationality. Apart from the scattered early cases referred to—in the Gold Coast, Guadeloupe, St Lucia, and so on—from the beginning of the latter half of the nineteenth century, 1851 to 1858, we have the French period, for it was by French physicians and in French territory that records are found almost exclusively during this period, in Madagascar first, but soon after in Senegambia, Senegal, Gaboon, Guiana and the French Antilles. Then, in 1858, came the Greeks with Varetta's description, followed a year later by American writers, first Cummings in Louisiana, next cases recorded in Alabama and Texas, and within a short period in several States. After this there was an interval of some years till the Italians, in 1874, took to recording cases, notably Tomaselli who saw patients in Sicily and the idea of quinine intoxication was adduced as a cause, soon after, cases were reported from Sardinia and Southern Italy. In 1881 Dutch authors began to record the condition in Java (Jacobs) and in

Guinea and New Guinea, the Germans in 1890 came to the fore, Schelling writing of it in Kaiser Wilhelm's Land, and being succeeded by A and F Plehn, Kohlstock, Steidel, Ziemann, Koch and others, and cases being reported in the Cameroons, in German East Africa, etc. Lastly, in 1898, came the British period, the investigation doubtless being stimulated largely by the work of Manson and Ross on malaria. A few of the names of observers and the places where they worked may be given. In *British Central Africa*—Moffat, Stephens and Christophers, Daniels, in *British East Africa*—Daniels, in *Nigeria*—Hanley, *Uganda*—Moffat, *Sudan*—Ensor, *India*—Seal, Powell, *China*—Wenyon, *British Malaya*—Wright, *British Honduras*—Brown.

J F Easmon in 1884 remarks upon the strange absence of the subject in British writings on diseases of the tropics and notes that it is not mentioned by Chisholm, Boyle, Clarke, Pym, Pritchett, Daniell, Horton and other writers on West African diseases. We have seen, however, that Boyle does refer to it (see p 253).

Bérenger-Féraud wrote that it was known in Dakar and Gorée from 1820, and between 1864 and 1870 there were 109 cases of *Fièvre bilieuse hémoglobinnurique* with thirty-five deaths and of pernicious malaria eighty-nine cases, fifty-one deaths. It must, therefore, have been present on the West Coast for many years, as the evidence adduced above shows, in spite of its absence from English medical literature.

At the present day, 1937, blackwater fever occurs in

Europe common in Greece, less common in Italy, Sicily, Sardinia, Russia and Yugo-Slavia

South-West Asia common in Palestine and Transcaucasia

India common in Bengal Duars, less in Assam, Bihar, Madras

Ceylon very rare, according to J W W Stephens only thirteen cases were recorded between 1913 and 1935, and six in the devastating epidemic of 1934-5. But in the returns given in the Annual Report of the Medical and Sanitary Services for 1936, 188 cases were treated that year in hospital.

Far East Upper Burma, Formosa, Cochin China, Tonking, Federated Malay States, rare in the Straits Settlements, Siam. A few cases in Java, Sumatra, the Philippines, Solomon Islands and the New Hebrides.

Africa all over the tropical and subtropical regions

North America in some of the States, notably Alabama, Arkansas, Florida, the Carolinas, Georgia, Louisiana, Mississippi, Tennessee, Texas, Virginia.

Central America Costa Rica, Guatemala, Nicaragua, Panama
Honduras and British Honduras, in the last there were
eleven cases in 1930
South America Brazil, Ecuador, Colombia Venezuela, British
and French Guianas
West Indies Cuba, Haiti, Jamaica (few), Guadeloupe, Trinidad
and Tobago (few)

All the world over, wherever blackwater fever exists, Europeans are the chief victims, but, as Megaw states, Bengali clerks in Assam tea-gardens suffer from it as do also the Egyptians in the Sudan. It would seem, therefore, that the disease is associated somehow with the more civilized conditions of living.

It is clear from the earlier synonyms of the disease that for many years the dark colour of the urine was not thought to be due to blood and later still that it was not blood itself, but blood pigment and its derivatives, in spite of the fact that the first record we have (1822) stated that the "urine has the appearance of bloody water."

Such noted observers as Bérenger-Féraud and Daullé thought that the colouring matter was bile, hence the name 'icteric pernicious fever' and Dutroulau's diagnosis *Fièvre bilieuse grave des pays chauds* in 1858, *Pernicieuse ictérique*, *Accès bilieux grave* (Lebeau) and, especially to be noted, *Fièvre jaune des acclimatés et des Créoles* in 1861. Others were non-committal, such as *Fièvre rémittente pernicieuse mélanurique* (Duchassaing, 1850), malignant malarial fever (Michel, 1869), *Fièvre à urines noires* (Pellarin, 1876), swamp yellow fever (Bailey, 1883), blackwater fever (Easmon, 1884), pseudo-yellow fever (Stone, 1900).

Others, again, believed that blood itself was present as is seen by the names Miasmatic hæmaturia (Cumings, 1859), *Fièvre ictéro-hémorrhagique* (Loupy, 1862), *Fièvre bilieuse hématurique* (Barthélemy-Benoît, 1865), Hæmorrhagic malarial fever (Michel, 1869), *Fièvre hémosphérinurique palustre* (Karamitsas, 1882), Malignant hæmaturia (McDaniel, 1883).

It was not until 1883 that we find a definite statement that hæmoglobin and not whole blood is present in the urine, in that year Corré speaks of *Fièvre hémoglobinurique*, and the connection with malaria is evidenced by the term malarial hæmoglobinuria, used by I. I. Jones in a letter to the *Medical Record* (1892), in the same year Kohlstock speaks of it under the cum-

brous name of *Febris tropica intermittens biliosa hæmoglobinurica*, and Davidson as yellow malarious fever with hæmoglobinuria, which is not much better. The association of the condition with quinine is seen in Barton's naming it hæmaturic cinchonism, in 1890, two years before it was recorded as due to hæmoglobin, lastly, in 1906 A Broden noted the presence of methæmoglobin, though thirty years before Louvet found that the urine gave a reaction indicating this in a paper entitled *De l'hématurie et de l'hémaphéisme dans la fièvre ictéro-hémorrhagique*, and C Heine-mann in 1885 found it by microspectroscope and definitely notes this in a paper with the title *Ein eigenthümlicher Fall von Methämoglobinurie bei Intermittens*, published in *Arch f Path Anat u Physiol u Klin Med*

Blackwater fever is historically interesting chiefly from the ætiological point of view. Suggestions have been many and most of these have been purely suggestions based largely on analogy and with little if any sound scientific foundation. Papers on the subject are legion, they number several hundreds, but the many theories can be grouped under four main headings

- 1 That Blackwater fever is a pernicious form of malarial attack
- 2 That it is quinine intoxication
- 3 That it is a disease *sur generis* or due to some specific organism
- 4 That it is an induced condition resulting from repeated malarial infection

1 That Blackwater Fever is a Pernicious Type of Malarial Attack

The early French observers, notably Lebeau, Daullé, Le Roy de Méricourt, Barthélemy-Benoît, Bérenger-Féraud, were of this opinion, and early American authors, Cummings, Osborn, Ghent, for example, did not, it seems, doubt it, for they called it 'malarial hæmaturia'

At first view there would seem to be much in favour, the disease occurred only in malarious countries, though, it is true, not in all, in other words, malaria could and did exist without blackwater, but not blackwater fever in absence of malaria. Stephens and Christophers in the Royal Society Malaria Reports, in 1900, showed that in a considerable proportion of cases parasites could be seen in the blood on the day after the onset of an attack. A Plehn, in 1895, had observed malaria parasites in the blood

of blackwater fever patients. In other cases, where not found after the onset Stephens and Christophers reported that they had been present on the day preceding the attack and often reappeared later, if parasites could not be detected other signs of malaria would be found, such as pigmented leucocytes, high percentage of large mononuclears, evidence in spleen or brain, etc. The fact that in certain places malaria was rife but blackwater fever was not seen, or at least was very rare, was accounted for by the suggestion that a particular species of the parasite might be the cause, or that a special vector might be incriminated (Daniels) so that the ordinary parasite gained in virulence or acquired its blackwater-producing properties by passage through such species. No evidence could be obtained of a special form of malaria parasite except that blackwater fever was in the vast majority associated with the subtertian plasmodium, this, however, was present in a much greater number of persons without causing blackwater fever. Nocht postulated strains of malaria parasites possessed of special hæmolytic powers. It is certainly the fact that subtertian malaria is more serious and more refractory to treatment in one place than in another, and James, Nicoll and Shute in 1932 showed that infections experimentally produced in monkeys by Roman strains were more severe than those produced by Indian strains, and it took nearly eight times as much quinine to control the primary attack and the fever lasted for a longer time. We know for a certainty also that Indian coolies brought up in a malarious district and infected from childhood, when brought to a fresh country, for example as indentured coolies to Jamaica, may suffer very severely from malaria and may exhibit blackwater fever.

In recent years Greek writers have again brought forward evidence to support the theory of a special strain or variety of *Plasmodium falciparum* being the cause of blackwater. In parts of Greece, they say, blackwater fever is endemic. In certain districts, towns or villages the malarial endemicity is practically the same, the inhabitants live under the same conditions, are of the same race, but only a certain number are attacked by it, persons living in particular places, and the number of cases varies from year to year. Several may be attacked in one house, though the victims are not related [here we may recall the 'blackwater fever houses' in Rhodesia investigated by J. G. Thomson in 1922-3]. Thus C. A. Dimissas, in a paper read at the Panhellenic Medical Congress at Thessalonica in 1935, reported that in 1930 he had been called upon to deal with an epidemic of the disease

at Comotini, in which there were sixty cases limited to a certain quarter of the town, at other times (in 1928, for example) cases had been confined to Parikia (Pasos), to Néa Péamos, in Chalkidone eighty-eight cases of blackwater fever occurred though there were none in the neighbouring villages, at Marpissa he saw none among 200 patients with malarial cachexia, at Acgkinion there were none among 1202 cases of malaria investigated, but in other villages of the same district there were fifty-seven among 6585 patients investigated, and at Perris seventy-six cases of blackwater fever among 4000 with malaria. Dimissas on these grounds argues in favour of blackwater fever being a nosological entity, due, he suggests, to a hæmolytic strain of *P. falciparum*, the pathogeny being that those who react well to small infections of blackwater fever acquire an immunity or a state of premunition, whereas those who do not react well or in whom the premunition is exhausted or reduced—as, for example, by cold, over-exertion, quinine—develop the typical blackwater fever.

Foy and Kondi have quite recently (their results were published in 1936 (*Ann Trop Med and Parasit*, December)) been carrying out researches into the question of a special hæmolytic strain of the malaria parasite, or other specific parasite, in setting up blackwater fever. They inoculated sixty-eight mental patients, as in the usual manner of employing malaria therapeutically, with Anophelines—*A. elutus*, *A. superpictus* and *A. maculipennis*—which had been infected from thirty-five cases of blackwater fever, and also inoculated 106 such patients with malaria-positive and malaria-negative blood from fifty-eight cases of blackwater fever. In no instance, though the patients were observed for periods up to eighteen months, did blackwater fever develop.

The condition is usually associated with *P. falciparum*, but some have found the other forms, benign tertian and quartan. In this connection we must bear in mind that the subtertian parasite may be seen at one time and the others later, even though there has been no opportunity for reinfection, at other times either the benign tertian or quartan and not the subtertian at a single early examination.

A useful piece of research would be to determine more widely than has been done the relative incidence of the different parasites in regions where blackwater fever is endemic. This has been undertaken in a few districts only. Thus, in 1910 Rogers determined it for Calcutta and found 54·2 per cent malignant tertian, 38·6 benign tertian and 7·2 quartan, in Bombay the relative

percentages were 46.0, 52.6 and 1.4 respectively. These and others are given in the following table

Place	Percentages of		
	<i>P. falciparum</i>	<i>P. vivax</i>	<i>P. malariae</i>
Calcutta (Rogers)	54.2	38.6	7.2
Bombay	46.0	52.6	1.4
Bareilly, U. P.	—	90.0	—
German East Africa (Koch)	89.0	—	—
Kenya Colony*	80.0	—	—
Rhodesia	93.1-96.0	3.0-5.0	1.0-1.7
Sierra Leone (various observers)	77.7-98.5	0.4	4.5-21.9
Sekondi	56.8-72.5	11.1-18.4	16.4-25.9
Accra	87.6	5.2	7.2
Jamaica (Scott)	81.0	9.8	9.2

* It is worth noting that perusal of past records in Kenya shows that in 1916-18, when Indian troops were introduced, *P. vivax* infections increased. After they were withdrawn conditions reverted to the previous state with large preponderance of subtertian parasite infections.

All that can be said at present is that, broadly, where subtertian malaria greatly preponderates blackwater fever is prone to occur. In Ceylon, though malaria is very prevalent, the subtertian parasite is found in about 10 per cent. only and except for imported cases blackwater fever may be said to be practically unknown there (in 1936 twenty-nine fresh cases were admitted to hospital, see also above, p. 256).

As regards the second alternative mentioned above—the special vector—this has recently been again advanced by Strickland and Chowdhury (1930)—that the species of *Anopheles* may modify the malaria plasmodia and make them more apt to provoke blackwater fever.

In 1897 Cardamatis and others in Greece and Tomaselli in Sicily noted the part which quinine seemed to play, maintaining that quinine might be the proximate cause, the onset certainly followed closely *post hoc*, but they held that a predisposition resulting from chronic malaria was a necessary preliminary and Koch definitely was of the opinion that blackwater fever was in no sense an attack of malaria but was rather quinine intoxication in a malarious subject (see later).

The interrelation between malaria and blackwater fever may be considered from several angles, such as geographical distribution, seasonal incidence, presence of parasites, type of parasite

most involved, endemic index in areas affected, presence of non-immunes, length of residence, mode of treatment of malaria, and so forth

The earliest records of value which compare or correlate malaria and blackwater fever epidemiologically are those of W J Deekes and W M James at the Ancon Hospital, Panama. They analysed the large number of 40,928 patients admitted on account of malaria and 232 admitted with blackwater fever during a little more than six years. They found that the latter part of the wet season was for both diseases the time of greatest intensity. Stephens found the same to hold good for Nigeria between 1899 and 1911, and Macfie and Ingram for Accra in 1917, and J G Thomson in 1922-3 in Southern Rhodesia. In the last the correlation is more closely shown because the seasons there are more defined. Thomson gives the admissions monthly for malaria and blackwater fever over a period of ten years, from which the following figures are taken

	Jan	Feb	Mar	April	May	June	July	Aug	Sept	Oct	Nov	Dec
Malaria	642	778	1153	1265	920	478	279	196	139	198	243	317
Blackwater fever	20	42	61	90	90	74	41	27	11	12	11	13
Per cent	3.1	5.4	5.3	7.1	9.8	15.4	14.7	13.7	7.9	6.0	4.5	4.1

Figures compiled by L S Dudgeon relative to the troops in Macedonia are at variance with the findings of Thomson in Rhodesia, but, as he remarks, the factors to be considered in war-time differ too greatly from those of permanent residents in endemic areas for any valid deductions to be drawn from them. Incidentally, Dudgeon found that blackwater fever appeared when malignant tertian malaria was at its lowest and the time of low death-rate from malaria was that of high blackwater fever incidence.

During the forty and more years since the clinical relationship between the two conditions was remarked upon by Plehn and he found the parasites in the peripheral blood, evidence that malaria is the primary cause of blackwater fever has steadily accumulated. It would be useless to name those who have confirmed this, for the list would include practically all who have studied malaria. The chief argument advanced against it is, or rather was, the fact that parasites might not always be found at the onset, but Thomson and others have shown that examination of films from cases of undoubted malaria may at times yield no

result, even though quinine has not been taken. Thus, Deekes and James in 1911 found among 40,928 diagnosed as malaria only 23,410, or 57 per cent, with parasites in their blood films.

2 *That Blackwater Fever is Quinine Intoxication*

There is a popular belief which has prevailed in many countries, and still prevails, that blackwater fever has become known only since quinine was introduced—such belief has, of course, little or no evidential value and in principle is a fallacious method of arguing, of more value is the fact that many patients attribute their attacks to a dose of the drug taken shortly before the symptom was noticed. The hæmorrhagic form of malaria [*i.e.* blackwater fever], says Hirsch, had, as regards Europe in his day, been recorded only in Sicily, though earlier in the tropics, and in 1877 Tomaselli stated that in Catania he had observed patients who had suffered for a long time from malaria fever and had used large quantities of quinine, and that such patients might present this symptom of hæmaturia [hæmoglobinuria] and that he ventured to regard this complication as a result of quinine poisoning—purely a suggestion.

Stephens and Christophers in 1900, and Christophers and Bentley in 1908, carried out experiments to test the possible mode of action of quinine in producing blackwater. They found that concentrated solutions of quinine would *in vitro* hæmolyse both normal red cells and those from blackwater fever subjects, but that cinchonized serum from a healthy subject, the serum being from blood withdrawn after 2 grammes of quinine had been taken, had no effect on the cells of a blackwater fever patient. Barratt and Yorke compared the effects of quinine in saline and in normal serum and found that whereas the former would cause hæmolysis, none was caused by its action on healthy red corpuscles in the presence of serum until the concentration of quinine reached 0.5 per cent, the equivalent of 25 grammes per five litres of blood. Evidence goes to show that direct hæmolytic action of quinine alone in the circulating blood plays no part and the action, if there is any, must be indirect.

Several investigators have contributed to our knowledge in this respect. The work of Stephens and Christophers (1900), of Christophers and Bentley (1908), of Barratt and Yorke (1909), of Ramsden and Lipkin (1918), of Dudgeon (1921), and Kligler (1923) seems to show that the direct hæmolytic action of quinine alone in the circulating blood plays no part in the hæmolysis, that there must be some added factor. Experimentally a dilution of

1 in 25 of bile in the blood resulted in prompt laking, but 1 in 50 and higher dilutions did not, if, however, with these higher dilutions, quinine was added, 0.02–0.03 per cent, laking was an invariable result

We must remember also that in actual practice quite a small dose may precipitate, or perhaps it would be wiser to say may be followed by, hæmoglobinuria. There may, of course, be a quinine hæmoglobinuria distinct from that of blackwater, but if so there are at present no criteria known to us by which we can distinguish them. Bastianelli in 1899 asserted that blackwater fever occurs only in those infected by the subtertian parasite, and he summed up the position by saying that "preceding malaria creates the fundamental disposition, existing malaria the accidental disposition, the quinine the provocative agent"

Again, although a survey and analysis of clinical records indicate quinine as a most important factor in the ætiology of blackwater fever, cases undoubtedly occur where no history can be obtained of the attack having followed shortly after the taking of quinine, moreover, other alkaloids of cinchona, such as cinchonine, and also plasmoquine seem to have precipitated an attack. Ziemann in 1900 maintained that blackwater fever occurs at times in negroes who have never taken quinine.

We must bear in mind that blackwater occurs in a malarious country and that in nearly every case, therefore, we shall have a history of the taking of this drug. The history in the vast majority of cases is that quinine has been taken for a long time (perhaps not very regularly) and then one day the taking is followed by an attack of blackwater, later the drug may have no such effect. Other patients, but these are rare, may affirm that quite small doses may regularly bring on hæmoglobinuria. H. Foy and A. Kondi reported in 1937 three cases in which blackwater fever supervened during or after treatment of malaria with normal doses of atabrin. None of them had taken quinine within two to nine months before and therefore quinine can have played no part in precipitating the attack. In two of the patients no parasites could be found at the time the hæmoglobinuria appeared, either in thick films of blood or in material obtained by puncture of the spleen. This, as Warrington Yorke has stated, throws doubt on the hypothesis that blackwater fever is associated with sudden destruction of large numbers of parasites and this writer regards it as highly probable that any drug which is of value in the treatment of malaria may be likely to precipitate an attack of blackwater, quinine being especially notorious because it is employed on

a vastly greater scale than any other drug. In this connection mention may be made of a patient in Lower Burma who developed hæmoglobinuria following administration of plasmoquine, 0.04 gramme daily as a prophylactic, at the end of the fourth day. In this case, however, there was no history of previous malaria, the blood showed no parasites and the spleen was not enlarged. It is uncertain, therefore, whether this was purely a toxic effect, unconnected with malaria and true blackwater fever (Min Sein, *Ind Med Gaz*, Feb 1937).

We may sum up the matter by saying that quinine was in use for treatment of malaria for some two centuries before we find any mention of blackwater fever in medical literature. The relationship was noticed first in 1858 by Varetas and Konsola. In 1874 Tomaselli laid stress upon the association and therefore more study was given to quinine as a precipitating agent or factor. In 1898 Koch, according to some authorities, brought forward the theory that blackwater fever was due to quinine poisoning, J. G. Thomson, however, states that Koch has been misunderstood, for he believed in quinine as a prophylactic of malaria and a preventive of blackwater fever. This unfortunate interpretation of Koch's views has done not a little to delay the timely use of quinine in malaria and malarious countries.

Others, again, suggest—it is little more than a suggestion—that though quinine in the usual doses has no action on healthy red cells, when they break up the liberated hæmoglobin becomes changed to methæmoglobin which is excreted by the kidneys as a foreign substance. Ziemann assumed (1900) that there must be a predisposition to blackwater fever—an assumption which, unexplained, does not help much. Granted this, he states that the condition may arise either (i) In the course of an attack of malaria without quinine having been given (ii) In a similar case which has been treated by quinine (iii) In patients who have recovered from an attack of malaria, who have no parasites discoverable in their blood, but who are still taking quinine (iv) In those in like state but who are no longer taking quinine.

Quite recently, in 1937, experimental work was undertaken in India (*Rec Mal Survey of India*, June–Sept, 1937) which throws a little light on this difficult question. Series of *rhesus* monkeys were infected with *P. knowlesi* and divided, for treatment, into three groups: one was treated with quinine sulphate alone, the second with methylene blue alone, the third with the two combined. From the effects produced it was observed that when the infection was at its height quinine might expedite the onset

of hæmoglobinuria which might, or might not, occur in untreated controls. As regards the second group administration of methylene blue was thought to prevent development of hæmoglobinuria but not to have any effect on the plasmodia. The only conclusion from combining the treatments was that it cured *P. knowlesi* infection in *rhesus* more readily than did quinine alone.

3 *That Blackwater Fever is a Distinct Disease, a Disease sui generis, due to some Specific Organism*

Craig, in 1911 (but, as we shall see shortly, he was not the first), suggested that blackwater fever was a disease *sui generis* on the following grounds. That all malarial districts are not places in which blackwater fever occurs, that cases are often confined to limited areas, even houses, within a highly malarious zone [but Thomson in Rhodesia showed that 'blackwater fever houses' were situated close to breeding sites of mosquitoes and were heavily infected], that it sometimes appears in epidemic form, though generally cases are few when compared with the percentage of malaria in a community, that the symptoms are characteristic, hæmoglobinuria occurring with each relapse, thus differing from the protean manifestations of pernicious malaria, that the pathology is distinctive, and, finally, that in many cases no malaria parasites are found. Whether the causative organism was protozoal, bacterial, or a virus was not proved.

Probably the earliest to postulate a protozoal organism was Sambon who, in 1892, suggested, on the analogy of blackwater with red water of cattle and dogs due to piroplasma, that a special organism of the same group, *Babesia*, might be the cause. But the animal disease, red water, seems to be due to the direct action of the parasite and the degree of it depends more or less on the number of piroplasma present, whereas in blackwater fever there is some indirect action due to chronic malaria over a long period, the condition is due, not so much to infection, as to repeated attacks and reinfections. Newcomers are not attacked and it is difficult to understand why they should escape if the disease is due to some specific organism, when they are living under the same conditions and exposed to the same risks as the older residents who are the ones to suffer. Sambon reiterated his view in 1898, disclaiming that blackwater fever has any relation with malaria and wrote strongly against the idea that quinine could cause it. In 1908 C. P. Lukis held that the second and hitherto undiscovered factor was the Leishman-Donovan body [despite

the fact that these bodies are not found in blackwater fever cases]

P J Foran in 1910 described a 'parasite of blackwater fever' which he had found in many natives, generally young children, and in Europeans also. He thought it was a *Piroplasma*. Again, in 1920, E Hassell Wright recorded cases in Coorg, Western India, and published plates of his findings in the *Indian Medical Gazette* in support of his view that in blackwater fever a special piroplasma infection occurs in addition to the malaria plasmodium, and he maintained that blackwater fever was a distinct disease due to a different protozoon from that of malaria, at least a necessary subsidiary. If not a piroplasma the parasite seen by Wright was thought by him to be a new and undescribed species of '*Laverania malarie*' (a synonym of *P falciparum*). These, however, proved to be but small forms of this plasmodium.

Next in order come the *bacteria* theories. The earliest of these is that of Bréaudat who in 1896 reported finding *Bact coli commune* in the blood of five cases at Tonking. Yersin had noted the same a year before. Others reported the presence of *Streptococcus*, *Staphylococcus aureus*, *Bacillus perfringens*, in the blood or spleen of patients. Cardamatis in 1902 in Greece, and Boinet in Indo-China, described a streptococcus found in the blood of a chronic malaria patient with an attack of blackwater fever. Later, in 1919 among the British troops in Palestine there were eighty fatal cases of malaria and in one a generalized infection with *B perfringens*, which appeared (Fairley and Dew) to be connected with an attack of blackwater fever coming on eighteen hours before death.

In 1912 Leishman reported finding and gave descriptions of inclusions in large mononuclear leucocytes and endothelial cells in cases of blackwater fever, which he spoke of as *Chlamydozoa*. In the following year A C Coles noted the presence of "granular blue bodies" intracellular and resembling the Koch's bodies, which occur as a stage in the life-history of *Theileria parva*—a reversion to the Babesia theory of Sambon, twenty years before. Also in 1912 Ashburn and Vedder described in Manila a patient with blackwater fever in whose blood they found a spirillum, but this does not appear to have been followed up. In 1918 came the *Spirochæte* theory which had rather a longer vogue. In that year Schuffner found spirochætes post mortem in the blood and organs of a patient dying with the clinical symptoms of blackwater fever. In 1922 Blanchard and Lefrou gave details of their triple-centrifugation method of obtaining what they denominated *Spirochæta*.

bilohæmoglobinurice Blood was taken into citrate solution and centrifuged, most of the red corpuscles being thus thrown down, the supernatant fluid was drawn off and again centrifuged whereby the remaining red and white corpuscles and the platelets were removed, the supernatant fluid was once more separated and centrifuged. The deposit was seen to contain occasional red cells some platelets and 'spirochætes' 6-9 microns in length and 0.1-0.2 in width. They showed irregular thickenings in their length when stained by Leishman's modification of the Romanowsky stain. Blanchard and Lefrou inoculated guinea-pigs intraperitoneally with this deposit and the animals died with abdominal distension, but no jaundice or hæmoglobinuria, similar spirochætes were found in their livers. This organ was emulsified and injected into another guinea-pig, this too died and at autopsy spirochætes were found in the lungs and the blood, but not in the liver. The lung tissue was emulsified and injected into a third guinea-pig, with like result. Blanchard and Lefrou thought that blackwater fever might be due to various causes of which this spirochæte was one. J. G. Thomson examined cases in Rhodesia, following exactly their technique, but came to the conclusion that these so-called spirochætes were merely filaments such as are to be found in the clotted blood, even of normal persons, the stouter filaments of 5-9 μ in length being derived from degenerate or damaged red corpuscles and the finer and longer from platelets. He concluded that their apparent motility was due to surface tension or currents in the fluid beneath the coverslip. His inoculation experiments failed to confirm those of Blanchard and Lefrou. Franchini and Maggesi gave some support to the theory in 1925.

The spirochæte theory died hard, in 1930 L. Soromaño found them in the gall-bladder and in the fæces during the stage of fever and postulated a hæmolytic form of the organism as causative, it was not found in the blood-stream nor in the kidneys.

The idea of some form of *toxin* came under discussion in 1915 as the result of investigations by Christophers and Iyengar into the effects of hæmolytic drugs, toxins and antisera upon the hæmolytic (isotonic) point and the association between this and the hæmoglobinuria. They tested chlorate of potassium, carbolic acid, sodium glycocholate, sodium taurocholate, pyrogallie acid, aloin, quinine, diphtheria toxin, pyocyaneus toxin and hæmolytic serum, and found that hæmoglobinuria resulted from pyrogallie acid, aloin and hæmolytic serum, all of which raised the 'hæmolytic point,' but not until that point reached 1.0-0.9 per cent did hæmoglobinuria appear. This was of academic interest mostly,

however, if not entirely seeing that they did not find any distinct raising of the hæmolytic point in blackwater fever. Negative evidence, nevertheless, has often much value and their work goes to prove that the process of production of hæmoglobinuria in blackwater fever is probably quite different from the action of these toxins. Three years later, in 1918, the question again came up when L. G. Parsons and J. G. Forbes recorded that in malarious subjects there might be a *transient* hæmoglobinuria with nausea, vomiting, shivering, loin pain and slight fever, passing off in twenty-four hours or so, following closely on exposure to cold and followed itself by passage of numerous urinary casts. They ascribed the condition to a special toxin in the blood, secondary to malarial infection.

4 *That Blackwater Fever is an Induced Condition brought about by Prolonged or Repeated Malaria Infection*

The almost unvarying history of patients is 'repeated attacks of malaria and irregularity in taking quinine'. The fever is often not the typical attack but chills and 'occasional touches of fever'. An investigation of the length of residence in an endemic area before the first attack of blackwater fever has been made by several. Stephens's analysis of 1050 cases showed that the majority occurred in the second and third years. J. F. Gaskell's experience in Macedonia affords a good instance of the tendency or liability to increase with length of residence. He records that among the Serbian Army during their first winter in Salonika there were no cases of blackwater fever although the incidence of severe malaria was high. In the following autumn and winter, by which time the troops had become saturated by two seasons of malaria, cases occurred associated with benign as well as malignant tertian parasites. In chronic malarious subjects blackwater fever tends to be a winter disease which is predisposed to by cold. His experience was, of course, in a country in which hot and cold seasons were very distinct, which is not the case in the tropics. In Gaskell's view the relation to quinine is very definite, each patient tending to have a "critical exciting dose," while smaller doses were beneficial. The precipitation of an attack by cold is exemplified by the onset in chronic malarious subjects arriving in England in the autumn or winter after years in the tropics. The 'critical dose' of quinine calls for proof, unless the susceptibility threshold is variable, for quite a small dose may be followed by an attack in a person who on previous occasions has been in the habit of taking the average dose.

Neither race, age, nor sex has any appreciable influence, though rare in indigenous natives in a blackwater fever area, if natives are brought from places where the endemic index is low they may develop blackwater

Seeing that in blackwater fever the urine contains not blood but hæmoglobin or methæmoglobin or other blood colouring matters (the so-called pseudo-methæmoglobin of Fairley), it is obvious that hæmolysis must have occurred somewhere and somehow. It is not strictly logical to separate this question from the foregoing, for each of the reputed causes—*Babesia*, streptococci, spirochaetes, etc.—was thought to set up hæmolysis, but the suggested modes of production of the hæmolysis have been many and for the sake of clarity and brevity they may be dealt with together. Some of them are pure conjecture, little supported by evidence and may be disposed of in a few words. Thus, Thayer, in 1898, stated that in malaria the red corpuscles were less resistant to osmotic changes in the plasma, but Stephens and Christophers showed that these cells had a greater resistance during the attack than had the normal cells, though persons living under conditions in which blackwater fever was likely to arise might have corpuscles with lowered resistance. In this connection, it is of course possible that the less resistant had been destroyed in the attack, leaving only the more resistant which would explain the findings of Stephens and Christophers and would not demolish Thayer's hypothesis. Next we have McKay's theory of "demineralization of plasma" based on his observation that even a single dose of the sulphate of quinine might reduce the salt content of the plasma, that is its hæmosozotic value. This effect was due, he said, not to the base, the quinine, but to the acid and that other salts, the bisulphate, hydrochloride, etc., would not have this effect, or at least to a smaller degree. McKay's paper appeared in 1908 and dealt with the action of quinine salts on the osmotic pressure of the blood plasma, by lowering this a disruptive force is exerted on the envelope of the red cells causing them to break and extrude their hæmoglobin. He found that sulphates in any form, magnesium sulphate equally with sulphate of quinine, or even dilute sulphuric acid, decrease the total salt concentration of the serum and this action is further facilitated in corpuscles already damaged by malaria parasites. Since, however, in many cases no such action was found, the suggestion of difference in virulence of parasites was adduced. It was thought that the sulphates acted by displacing weaker acids—carbonates, chlorides, etc., combining with their bases to form sodium and calcium

sulphates, and these being foreign to the plasma are eliminated and the blood becomes poorer in alkalies and total salts. Chlorides be found to have an opposite effect, the red cells hæmolysing with greater difficulty after they had been taken, hence the suggestion to substitute the chloride for the sulphate of quinine.

On the other hand, blackwater fever may follow administration of these other salts and the fact, even if true, would not explain the immunity of the new arrival from attack. Others have suggested that the malaria parasite might secrete a specific hæmolysin, analogous to the anæmia of ankylostomes, for this again there is no evidence and the theory is but a variant of there being a specific form of parasite referred to above. Balfour, in 1913, suggested that the proximate cause might be the injection of a highly virulent hæmolysin by some insect—purely hypothetical and unsupported by any evidence, but as a theory might be, as Thomson stated, worth investigation. This, again, would not explain why new arrivals escape.

Hintze in 1916 thought that light might play a part, its hæmolytic action being aided or reinforced by sensitizing substances such as quinine salts, bile pigments, blood pigments, in particular hæmatoporphyrin. His view was supported by Hewetson (1922) who suggested that in Southern Rhodesia blackwater fever tended to occur in houses which were imperfectly protected from the sun, those, for example, with roofs of corrugated iron. Again, why should new arrivals escape?

In 1928 Blacklock and MacDonald proposed a theory that stasis of blood in the spleen, which occurs in malaria and is ascribable to plugging of the sinuses with parasites taken up by the reticulo-endothelial cells, leads to an anoxæmia with consequent lactic acid formation which favours hæmolysis. Exertion, chill, quinine might thus precipitate an attack by causing contraction of the spleen. Some twenty years before Christophers and Bentley studied from many angles the conditions under which hæmolysis takes place and the various constituents of and changes in the blood in blackwater fever. They ended by excluding parasitic, osmotic and chemical actions as ætiologically active and came to the conclusion that the condition was due to some specific hæmolysin arising within the body—hæmolysin not derived from the parasite, but “thrown out as a result of the constant phagocytosis of red cells” (*Scientific Memoir, No 35, Medical and Sanitary Department, Government of India, 1908*). Assuming the malarial origin of blackwater they ask, “Why is not hæmoglobinuria seen in severe malaria?” and reply that it is because the red corpuscles

are phagocyted in the spleen—erythrokatalysis—and this is characteristic of malignant tertian infections, not of benign or quartan, then resorption of the products of destruction result in formation of an autohæmolysin

J O W Barratt and Warrington Yorke in 1909, when writing on the development of hæmolytic amboceptors in the blood, expressed the view that chill, exertion, quinine, act by producing “an explosive development of complement”

A Plehn in 1920 put forward a theory which at first seemed to simplify this complex question and, had the fundamental principles, or better postulates, been sound the superstructure would have been not only imposing but satisfying. His view was that the presence of malaria parasites was a primary essential, during an attack of malaria fever there is a rapid destruction of these and the body is rendered hypersensitive to the protein of the malaria parasite. The giving of quinine or the use of any other means by which destruction of a few more parasites is brought about precipitates a crisis—analogous to an anaphylactic shock. Hæmolysis does not arise in the blood-stream because hæmoglobinæmia is not present as a rule, he maintained, nor does it arise in the hæmopoietic organs, bone-marrow, spleen or liver, but in the kidneys. There is loss of renal epithelium the result of which is an abnormal relationship between the tubules and the contents of the blood-vessels, the renal secretion becomes hypotonic and thus has a hæmolytic effect on red cells which urine in health has not.

On the other hand, it was shown by Christophers and Bentley in 1908 and by Barratt and Yorke in 1909 that hæmoglobinæmia does occur, that it is present in normal persons to the extent of 0.1–0.15 per cent, that just prior to the passage of ‘blackwater’ this increases to 0.3, after passage it may be three times as great, from 0.3 to 0.95 per cent, whereas during passage it may be no greater than in health, but on occasion is a little above, 0.09–0.25 per cent.

L S Dudgeon in 1920 found that the hæmoglobinæmia rapidly falls and “may be overlooked unless the examination is made at the correct moment”

Again, as regards the supposed hypotonicity of the urine which is a marked feature of Plehn’s hypothesis, investigation shows that the specific gravity is not very low and in fact may not be below normal. Yet again, the changes described by Plehn in the renal epithelium and the denudation of the tubules are not found generally to be precursors of blackwater fever, on the

contrary, experiment carried out by Barratt and Yorke in 1911 supports the view that the changes in the epithelium are secondary to the passage of hæmoglobin through the tubules

Thus, Plehn's theory of a primary renal lesion with hæmoglobinuria as a secondary phenomenon breaks down on examination. As Yorke writes in 1922 in a review of this question

Profound degeneration of the renal epithelial cells is not found, and the granular detritus and casts seen in the urine and renal tubules are not derived from disintegrated epithelial cells. Dislodgement of the epithelial cells and such degeneration as does occur is a secondary matter and probably due, in part at least, to mechanical causes. The serum proteins and red cells which are found in the urine in some cases of blackwater gain access to the tubules through the lesions produced by dislodgement of the epithelium

Thomson, from his researches in Southern Rhodesia in 1922-3, put forward the theory that the chemical changes occurring in the red cells which led to the production of 'brassy corpuscles' might result in these acting as foreign bodies and producing a specific hæmolytic amboceptor which in the presence of complement can act upon corpuscles so changed

The most recent view, that of Fernán-Núñez (1936), that hæmoglobinuric fever is an allergic phenomenon in part repeats that of Plehn, they travel in the first stage of the journey along the same line. Fernán-Núñez's theory is that a non-immune person has an attack of subtertian malaria during his first two years in a malarious district. This attack may produce immunity, but if the immunological process goes wrong sensitization may be produced. A subsequent attack of subtertian malaria produces an allergic reaction with destruction of the sensitized red cells. One attack predisposes to another. Whether immunity or allergy will occur in an individual will depend to some extent at least on the general health. Lowered resistance, the result of malnutrition, chronic organic disease, debility, alcoholism, excessive fatigue, chill, excitement, and so forth may thus provoke attacks of blackwater fever

Such allergy could result from sensitization by protein antigens of the malaria parasites, the allergic attacks being precipitated by a re-infestation or reactivation of a latent infection of the same species, or strain, of plasmodium. Quinine destroying the parasites might rapidly liberate allergens and bring on an attack, and it is a known fact that an attack can be precipitated by quite a small dose, regardless of the number of parasites and severity of the paroxysm, a like part may be played by atebirin

or plasmoquine In some instances the hæmoglobinuria may be due altogether to quinine allergy, blackwater fever is certainly more common in those with idiosyncrasy to quinine, he maintains

This, it will be seen, combines, as it were, many of the earlier theories or auxiliary factors which have been suggested from time to time *Diet*—Béranger-Féraud in 1874 thought that lack of fresh vegetables (as at Gorée) might be a cause, Jackson suggested that certain foods might act by throwing an unnecessary strain on the functions of the liver *Disposition*—Benoît in 1865 thought that long residence in a malarious climate produced a “bilious or sanguineous” temperament and malaria cachexia *Exertion and Chill*—Blacklock and Macdonald in 1928 *Climate* or change of locality—Gouzien in 1911, Parrot in 1915, and so on

Stephens in his recent work sums up the theories of ætiology—most of which have been considered above—under the following main heads

1 Accessory factors, such as alcohol, chill, diet, emotion, sun-stroke

2 Disposition, personal familial or environmental (as living in a ‘blackwater fever house’) may imply some unknown infective agent, but malaria cannot be excluded

3 Bacteria, spirochætes, protozoa (other than malaria) have in no case been *proved* to have any ætiological significance

4 Hæmolysins, anaphylaxis, sarcolactic acid, have been postulated largely as speculative opinions

5 Age, sex, race, occupation, length of residence may play a part, but what part is not known at present The relative rarity in Italy as compared with Africa, for example, may be due to the fact that in Italy subtertian malaria is an æstivo-autumnal infection, whereas in the tropics it prevails throughout the year, and hence, in the latter—workers on railway construction in the tropics, for instance—there is no intermission of infection Inasmuch, however, as these can be tested mathematically it ought not to be a very difficult matter to evaluate them

In short, there are several causes of hæmoglobinuria, at least several conditions in which this symptom may occur—Winckel’s disease in children, Texas fever in cattle, certain poisons, as by cobra venom, and so on The problem still unsolved in blackwater fever is the cause Malaria is at the back of it, but what is the proximate cause is still unknown Why, amongst hundreds of

endemic centres of malaria should only a few be centres of blackwater fever? Why, in such centres should there be hundreds of cases of malaria but only a few of blackwater fever? "What"—as Sir Patrick Manson used to say, "—what pulls the trigger?"

In paroxysmal hæmoglobinuria an autolysin can be demonstrated in the serum, but no success has rewarded efforts to discover it in blackwater fever. In this connection mention may be made of Achard and St Girous in 1912 and Gasbarrini in 1915, who reported finding an autolysin in the red corpuscles, but not in the serum in blackwater fever, also of Bijon who in 1915 found a corpuscular fragility, which Christophers and Bentley had shown in 1908 to be fallacious (v s). Browning suggests the elaboration of hæmolytic toxins from the tissues, for example the liver, resulting from damage caused by an infective agent or its toxin—again pure hypothesis—also it merely throws the question a stage further back and calls for further information as to what infective agent or what toxin. Others, again, have suggested a hæmolytic action on the part of the urine itself. This was proposed as long ago as 1865 by Pellarin, and later, in 1903, by Plehn, and in 1920 by Rowe. Dudgeon extracted hæmolytic substances from the urine of blackwater fever cases in 1920, but the sterilized secretion had no such effect when injected into animals.

Blacklock thinks, and it would seem with good reason, that the term 'blackwater fever' is too restricted and that more attention ought to be paid to pre-hæmoglobinuric states, also that mild attacks may be overlooked, especially if accompanied by slight jaundice and the presence of bile in the urine. Urobilin, we know, present in traces in normal urine, is increased in febrile states and markedly so in the early stages of a malarial attack. The normal 0.01–0.1 gm. may be increased in subtertian infections to 2.3 gm. in the twenty-four hours. de Jonge in 1904 found that when quinine was taken the output was still greater. Sorensen regards the increase of urobilin as indicative of a prehæmoglobinuric state and a sign that no more quinine should be given.

The mechanism of urinary suppression, believed by Plehn to be due to "nervous inhibition of glomerular secretion" was discussed by Warrington Yorke in 1911 (in the *British Medical Journal*). He believes it to be due to mechanical blocking of the tubules by granular material from the hæmoglobin. By animal experiment he showed that if the blood-pressure was lowered and hæmoglobin then injected intravenously, casts appeared in the urine, epithelium degenerated and the tubules became blocked. In severe cases there was complete anuria and death.

TREATMENT

There is little to be said, historically, as regards treatment. Many forms have been recommended, mostly by new arrivals and younger practitioners rushing to place on record a few cases, perhaps only a single case, in which some form of treatment has not been followed by death of the patient. One all-important fact is frequently forgotten, namely that many recover without any drug treatment at all. Some who report success in two or three, or half a dozen consecutive cases, if they were asked what results followed the same treatment in the succeeding like number, would be reluctantly compelled to admit failure and a reduction of their 'cures' to 50 per cent and as time went on to a still lower proportion. Hundreds of papers have been published dealing with the treatment of this condition, mainly valueless, except as instances of the *post ergo propter* fallacy, and based on claims scientifically quite without justification. Mere mention will, therefore, suffice for most of these forms of treatment.

Chronologically we may start with *quinine*. If blackwater fever is of malarial origin and quinine is a specific for malaria, it is logical to infer that it will do good in blackwater fever cases also. So argued Steudel in 1894, and many still support this line of reasoning. On the other hand, if malaria parasites are not seen, argue others, it is not only useless and illogical to give it but, if there is anything in the allergy and hæmolysin theory, it may do harm by destroying the few remaining parasites. In the same year, 1894, *transfusion* was used by Steudel in German East Africa with success, and since then many cases of its use have been reported with varying results. The next of importance in chronological order came *terebene*, introduced by Kerr Cross in 1901 and used fairly widely in Nyasaland, and many recovered after its use, since then, however, others have tried it without benefit. *Sodium bicarbonate*, 10 grains, with liquor hydrarg perchlor 30 minims, given every two hours for twenty-four hours, then three-hourly till the urine cleared was reported by Hearsey in 1904 as having been given to eighteen patients consecutively without a death. It will be remembered that Sternberg employed a similar combination for the treatment of yellow fever. In 1907 Gouzien, the principal medical officer of the French colonial troops in Dahomey, gave hypodermic injections of 0.7 per cent *saline*, at the suggestion of Reynaud. Later, others gave it in doses of 25 cc once or twice a day intravenously and intrarectally. Success, when it followed, was probably due to diuresis, which is

favoured by intravenous injection of saline. In 1908, Fontoynt reported that an infusion of *Aphlora thæiformis* (known locally as Voa-fotsy) had been used "for a long time" by the natives of Madagascar for blackwater fever, he does not, however, give any records as to its success or failure. Next in order came the use of *hypertonic saline*, in 1914, presumably based on Plehn's idea of the hypotonicity of the blood in these cases. The mixture consisted of 1.2 per cent NaCl and 0.03 per cent CaCl_2 , and two pints were injected *intra venam*.

In 1920 another vegetable preparation came to the fore in treatment of both malaria and of blackwater fever. J. C. S. Vaughan wrote of the promising results which he had obtained with watery extracts of the leaves of *Vitex peduncularis*, a plant growing in Chota Nagpur Province of India, which had for long been used by the natives for cases of fever. Its active principle has not yet been isolated.

It has been noted above that streptococci had been found in the blood and spleen of patients and that this was one of the organisms which had been regarded as causative. It is only natural, therefore, that antistreptococcus serum should be tried. There was another reason also, namely, that hæmolytic and anti-hæmolytic substances are both present in normal blood, but in blackwater fever and in paroxysmal hæmoglobinuria the latter are said to be deficient. Yet more, Cranford was of opinion that streptococcal septicæmia might complicate blackwater fever. On one or other of these grounds Ruiz in 1923 employed this serum in 20 c.c. doses. The uncertainty of blackwater fever remedies is well exemplified in this. At times there was a 'strong reaction,' at other times none, of six patients so treated one died, of six others receiving the same treatment three died. In 1924 ordinary horse serum was used, with a view to rectifying the deficient anti-hæmolytic substance in the blood of blackwater fever patients. Recently, there has been a reversion to the use of sodium bicarbonate with addition of glucose, this had been employed by Hamilton Fairley and R. J. Bromfield in 1934. They used 150 grains of bicarbonate to the pint and 5 per cent glucose, giving 17 oz. of the former and 13 oz. of the latter intravenously, and five hours later a pint of the former and 17 oz. of the latter.

In conclusion, a few words on prophylaxis. In 1932 G. R. Ross, in his account of his investigations in Southern Rhodesia, stated that the administration of sodium bicarbonate, which had been

lauded as a prophylactic by J Carreau in 1891 and A Guillon in 1909 prior to quinine had not led to "any diminution of the risk of hæmoglobinuria in quinine-intolerant cases" In those who can and are willing to take quinine regularly—and the regularity is essential—the drug seems to be the surest prophylactic The White Fathers in Nyasaland make it a rule to take 5 grains daily, and if any feels ill or tired this dose is doubled, in 1932 it was reported that during the previous twenty-eight years among 600 of them adopting this practice there had not been a single case of blackwater fever

Fernán-Núñez has proposed a method of prophylaxis based on his allergic theory referred to above (p 273) He prepares a suspension of parasitized erythrocytes by Bass's method and to this 0.4 per cent formalin is added Four hundred and ten persons of white or mixed race who had been resident for six months or more in the Lebrija Valley, Colombia—a blackwater fever district—received 0.2 c.c. of the suspension intracutaneously, and sixteen of them showed a local reaction within twelve hours characterized by a reddish discoloration, possibly hæmolytic, fading in a couple of weeks All who presented this reaction were removed to a non-malarious climate, that is, all such as showed a susceptibility by this allergic reaction, and "blackwater fever disappeared from the community" Further returns from this district will be awaited with interest

CHAPTER VII

YELLOW FEVER

I INTRODUCTORY EARLY HISTORY

The task of giving a connected account of the history of yellow fever and of research into this disease is by no means an easy one. After a long period during which nothing was known about yellow fever except vaguely its deadliness to Europeans, the fear it inspired in sailors and its menace to traders between West Africa and the West Indies and South American ports, when its diagnosis was uncertain and its nature entirely cryptic, as we infer from its many synonyms, a sudden spurt took place, a rapid stride in advance was made, stimulated by the suggestions of Nott, Beauprethuy and Finlay, the work of Reed, Carroll and Lazear, and the confirmation of their conclusions in practice by Gorgas.

As the result of this we thought we had found out all that was to be known, at any rate all that was essential for dealing successfully with yellow fever, we were convinced that if we could safeguard the mosquito from infection by keeping it away from a patient, or by isolating the patient from it during the period of infectivity—the first three days or so of illness—and reduce the number of mosquitoes or, better still, eradicate the tiger mosquito—the vector—and prevent the introduction of non-immunes till this was effected, the disease would be brought to an end. Of course, if either of the first two of these were successfully accomplished the desired result would be attained.

After another interval came reports of investigations and research, by Noguchi, Stokes, Young, Beeuwkes, Sawycr and others, each contributing something, the most important result being the knowledge of the possibility of transference of infection to animals and from this the evolving of a protective vaccine and later a 'protection test' to prove immunity and thereby cryptic or patent infection in the past. Next came the discovery of the existence of immunity—hence, previous infection—in parts of the world where the disease was not known to occur at that time, nor, so far as local knowledge was reliable, in the past.

Thus we found once again that Nature, after millions of years, does not give away her secrets too readily, that she keeps certain trumps up her sleeve, or shall we say as more polite and less suggestive of dishonesty, in reserve? The trick we thought was as good as won is overtrumped, or, to vary the metaphor, our house comes tumbling down, the foundation having been built in part securely on rock, in part unsafely on sand of whose presence we were unaware

Naturam expelles furca, tamen usque recurret,
Et mala perrumpet furtum fastidia victrix

Cases came to be reported proving the existence of infection in places where the transmitter *Aedes ægypti* was not to be found, where the people were not shore-dwellers, nor were they herded and overcrowded, but lived in rural districts, in jungle even, sparsely distributed. So the whole question which we believed had been settled for all time had to be opened up again and research started anew. By degrees knowledge is accumulating afresh—line upon line, precept upon precept, here a little, there a little—contributed by workers in different parts of the world, but especially by the medical staff of the Rockefeller Foundation or those working on their lines or in association with them.

All this will have to be related. The difficulty lies largely in the danger of swamping major points in a flood of minor details, of our not seeing the wood for the trees.

The logical method of beginning a history of yellow fever would seem to be to tell of its place of origin. This, however, is a matter which has been under discussion for some years and even now cannot be said to be settled. The arguments for and against Africa on the one side and America on the other have had to be greatly modified in the light of recent research, the older epidemiological ideas based on historical and chronological evidence have been to a considerable extent overturned by that afforded by modern immunity tests. Hence it has been thought wiser to postpone remarks as to the place of origin until the evidence on which present-day argument is founded has been narrated.

The term 'yellow fever' as applied to this condition seems to have first been employed by Griffith Hughes in 1750 in order to differentiate it from bilious remittent or other forms of malaria, in his work on the *Natural History of Barbadoes*. For nearly 200 years before that, however, though confusion with other diseases,

especially in the early victims of an outbreak, might arise—it does even to-day—the idea that the disease was a distinct one was clear in the minds of those who met with it. The legend of the *Flying Dutchman* describes a vessel doomed to haunt the seas around the Cape of Good Hope because, after a murder had been perpetrated on board, yellow fever broke out and no port would give her harbourage and all the crew perished. Coleridge's *Ancient Mariner* is also thought to depict a ship stricken by this disease. The ship *Huskisson* affords a contra-account to that of the *Flying Dutchman*, quoted by Dr Charles Singer, for this vessel was unable to leave harbour owing to an outbreak of yellow fever. This is an authentic instance which took place just a hundred years ago. The vessel was taking on cargo at Sierra Leone when yellow fever broke out among the crew and only two or three survived. The disease was also present in the town and for three months the captain was unable to obtain another crew. Offers of high pay, however, proved too tempting a bait and a fresh crew was then signed on. Whether they, or one of them, brought infection on board again, or whether the vessel still harboured infective mosquitoes cannot be stated, but the disease again broke out and again nearly all the crew perished.

Yellow fever has played a considerable part in the political history of the Caribbean. Dr Bird of Porto Rico relates that an outbreak of the disease is responsible for that island being now American and not British. In 1598 Lord Cumberland attacked San Juan, its capital, Porto Rico being then a Spanish colony. His fleet captured the city and for five months it was under his rule. He was planning to found a British colony there when a devastating epidemic of yellow fever broke out and forced him to leave the island.

Haiti, formerly called *Isla Española*, or *Hispaniola*, owes its independence as a Black Republic to an epidemic of yellow fever. At the time when Napoleon was taking steps to utilize Haiti as his base for colonizing and fortifying the territory of Louisiana the Haitians rose in revolt against the French rulers and put up a stubborn resistance to picked troops sent out in 1800 by Napoleon to subdue the country. The new arrivals were non-immune to yellow fever which wrought such havoc among them that the French were compelled to leave the country. Twenty-three thousand are said to have perished out of a complement of 30,000. "It was the irony of fate that this defeat of the French at the hands of the blacks came at a time when the all-mighty Napoleon was at the peak of his glory in Europe."

When the disease assumed epidemic characters its identity was doubtless generally recognized, but the earliest intelligible description known is that by Fray Diego Lopez de Cogolludo of an epidemic in Yucatán, Mexico, in 1649. There is, it is said, an account written by a French Jesuit in Guadeloupe in 1635, but we have not been able to trace this, nor even to discover the name of the writer. Some of the outbreaks of disease in the early days of the Spanish Conquest would appear from a study of the symptoms detailed to have been scurvy or one of its allies, rather than yellow fever. Suggestions have been made to identify the plague of Athens, described by Thucydides, with yellow fever. To discuss this now would take us too far back. Theoretically, it would be possible, for the extensive epidemic of dengue in Athens in 1927-8 (20,000 persons were attacked in 1927) shows that *Aedes ægypti* can thrive there.

The first to describe the disease in Africa was Schotte in 1780, who gave an account of the outbreak at St. Louis, Senegal, in 1778, which was traced to importation from Sierra Leone, but this sequence of dates must not be taken to mean that it existed in America (Cogolludo's account was given, as stated above, in 1648) before it occurred in Africa, the question of source and place of origin is discussed later. Others who have written on the subject and thought worthy of special mention by Fielding Garrison are John Bard, Mitchell in 1741, Colden in 1743, John Lining (1750) and William Currie (1793).

The first detailed account of any epidemic of yellow fever in the New World is probably that recording the Fever of Olinda, Pernambuco or Recife, a seaport of north Brazil in 1685-6. There had been many records earlier than this of epidemic diseases, modern investigators have tried to come to a decision as to whether these or any of them, and if so which, were yellow fever. We must remember that in the early days diagnosis was uncertain (this is considered in more detail below) and also that earlier accounts were written by laymen who used vague terms such as *una peste*, *una fiebre pestilencial*, *el contagio*, *la epidemia*, *la modorra* (the last meaning lethargy or stupor and, as this occurred in rural districts, is now thought more likely to have been malaria).

All the records of disease in the country covered by the Spanish Conquest may be divided into three groups. Firstly, Mexican records, kept before the Conquest (1519), chiefly by means of hieroglyphics and picture writing, and later by such writers as Motolinia (1524), Sahagún (1529), Diego Duran (born 1538) and Torquemada. Secondly, Nahuatl records which are fairly com-

plete for a century and a quarter, from seventy-five years before the Conquest to fifty years after—those of Gomara, Bernal Diaz, Oviedo and Herrera (1535) Thirdly, the Spanish historians Among all these there is no disease described bearing any resemblance to yellow fever, moreover, the outbreaks which are mentioned are ascribed to cold and famine and occurred in the *tierra fria*, the ‘cold country,’ where yellow fever, if introduced, would be unlikely to spread ¹

A few words may be said in reference to the chief of the epidemics recorded in the three-quarters of a century after the Conquest

- 1520 Tohtomonatzitli (to have pustules), almost certainly small-pox It affected the City of Mexico and proved so severe that Cortez abandoned the place
- 1531 Sarampión (measles), also very fatal, but less so than smallpox, among children the fatality rate was greatest
- 1538 Another outbreak of smallpox
- 1545 An outbreak characterized by fever and profuse hæmorrhages from nose, mouth and anus The mortality was indeed appalling It was said that in Mexico deaths numbered 800,000, in Tlaxcala 150,000, in Cholula 100,000, and large numbers, though less, in other towns
- 1550 Paperas (swelling of neck) A characteristic of this was a “close embrace around the throat, often ending in death” It seems to have been too severe for epidemic parotitis and was more probably a malignant angina with adenitis, perhaps diphtheria (the Spanish term for croup is *garrotillo*)
- 1563 Mathaltotonqui (bluish-green fever), probably the same as that recorded eighteen years earlier in 1545 and thirteen years later in
- 1576 Fever with hæmorrhages The epidemic was prolonged into and during the cold season, and Torquemada estimated that deaths totalled about 2,000,000 He stated that it was “*daba en tabardillo*,” that is, appeared like tabardillo, a spotted fever now known to be a form of typhus

¹ Much of the information available to those who are unable or have not the leisure to consult the originals or reproduction of them has been collated by Henry Rose Carter in his work *Yellow Fever an Epidemiological and Historical Study of its Place of Origin* Baltimore, 1931—a work full of interesting information from which I acknowledge to have borrowed freely —H H S

1588 A widespread and fatal famine

1595 A mixed outbreak of paperas and tabardillo, that is, anginose sore-throat and typhus

With exception of the outbreaks in 1545, 1563 and 1576, the diagnosis is fairly clear. Evidence is against any of these three having been yellow fever, for they raged in the *tierra fria* and were accompanied by an eruption (*matla*). They might have been hæmorrhagic smallpox or, more likely still, typhus, perhaps mixed with louse-borne relapsing fever. We may recall in this connection, the Dublin outbreak of 1826-7 described by Graves and that of Dundee and Edinburgh in 1843, described by Anott, Cormack and others.

The 1576 epidemic is graphically described by Father Sahagún who lived at the time. His account reads like Defoe's *Plague of London*, allowing for the relatively smaller population.

It lasted three months, many are dead and each day more die, increasing day by day, 10, 20, 30, 40, up to 80 a day. Many will die of hunger and of having no care. The monks walk from house to house, confessing and consoling them. If this goes on the race (Indians) will be entirely destroyed and the Spaniards not being able to hold it, the land will be left to wild beasts and forest.

We see from this that it was the Indians who were chiefly attacked, not Europeans—a further point against its being yellow fever.

In the second of the three groups spoken of above, Diaz de Castello notes epidemics of smallpox and others in which a characteristic symptom was "throwing off of blood by mouth and nostrils," similar to that described by M. E. Connor in Mexico and familiar to all who were practising in 1918, in the fatal epidemic, or rather pandemic, of influenza, when pneumonia set in as a complication. Connor was exceptionally well equipped for distinguishing it from yellow fever, for he was one of the investigators of the disease in Mexico.

Herrera in 1601 wrote of the unhealthiness of Vera Cruz [the place was so named by Cortez because he first landed there on Good Friday, 22nd April, 1519]. He notes the "difficulty of raising children," but this was due probably to malaria introduced by the Spaniards or negroes, since this disease may depopulate a community in which it is endemic, whereas yellow fever does not. In Herrera's work there is no disease mentioned which one could regard without doubt as yellow fever, either among those spoken of before the Conquest, or after it up to the time of his writing. The mortality at Vera Cruz is easily explained by malaria, dysen-

tery and other tropical conditions It was not found unhealthy in 1519 by Cortez or those who accompanied him, nor by those whom he left behind to garrison it when he moved on to Mexico

As regards Yucatán, Campeche and Guatemala, the temperature would certainly permit the breeding and activity of *Aedes ægypti*, the vector of yellow fever, at all seasons, also the population was sufficiently large and dense to maintain the infection, and the method of storing water on the premises would suit the mosquito admirably

Yucatán was visited by Columbus in 1502 In 1527 Montejo commanded an expedition from Spain *via* Hispaniola (now Haiti) to Cozumel and Salamanca, and among his men there was a heavy mortality, but we cannot find sufficient evidence to enable the cause to be identified It is unlikely, most unlikely, that it was yellow fever, because, in spite of many new settlements being made, there is no record of anything indicative of yellow fever during the succeeding hundred and twenty years In 1648 an outbreak which attacked both Indians and Spaniards, old as well as young, is recorded Consequently, if the former was yellow fever, as some maintain, it must have disappeared for a long period in spite of the establishment of new settlements and of the repeated introduction of susceptibles, while continuous commerce with the Gulf Coast and the Caribbean would have brought infected persons or at least infected mosquitoes if any were there to be brought We may infer from this that not only was Yucatán free from yellow fever at this time, but Cuba also and other islands having trade connection with Yucatán Finlay was of opinion that Cuba was not attacked by yellow fever until 1649

The 1648 epidemic at Yucatán may be looked upon as the first New World outbreak to be identified with certainty as yellow fever, thus this may be said to form the dividing line between 'traditional' and 'historical' yellow fever

In Mexico accounts give smallpox the first place among early epidemics, but towards the end of the fifteenth century (1477-1500) an outbreak is noted characterized by Xekik which means vomiting of blood Xekik seems to have been known to the Mayas in Yucatán before the Spaniards arrived, if we assume that records have been accurately interpreted This is by no means certain for the term used in the original is Maya cimil or 'Maya death' with pustules Seeing that the translation bears date 1648 it may be that the translator has 'read back' or read into the record Xekik (or blood vomit) as a gloss on 'maya cimil'

We may sum up this part of the investigation briefly thus

1 If yellow fever already-existed in Yucatán, Mexico, or Central America, the Conquest by introducing susceptibles repeatedly would increase the prevalence of the disease

2 If yellow fever existed in other parts of the coast or in the West Indian islands with which trade was carried on infection would be repeatedly introduced into Yucatán from without, even if it were not already present there

Therefore, since there is no evidence to show that Yucatán was infected until well over a century after the Spanish Conquest, it cannot have been an endemic focus, nor part of an infected region. Up to 1648 all the available records point to the outbreaks being of diseases known as European, such as smallpox, measles (*sarampión*), typhus (*tabardillo*) and perhaps scarlet fever, for an account of an outbreak in 1609 gives a clinical picture of scarlet fever included under the same name *tabardillo*. The 1648 outbreak described by Lopez de Cogolludo and referred to by Finlay in his *Trabajos selectos*, was undoubtedly yellow fever. It started in Campeche which was practically wiped out and then passed on to Mérida. The friars visited the town and brought back infection to their cloisters, and they fell victims after the usual incubation period. The description is graphic and typical. The patients were seized with severe pain in head and body generally.

Soon after a most vehement fever, with in some cases delirium and vomiting as of putrefied blood. To most the fever appeared to remit entirely on the third day and the patients said that they were free from pain, delirium ceased and, although they said they were well, they could not take nourishment and most died on the fifth day.

The vomiting is not an early symptom as a rule, though described so here, perhaps it is mentioned early in this old record because of its prominence and not because it appeared in the first stage. Clearly, the infection must have been unusually severe if death occurred in most cases on the fifth day, in more recent outbreaks the fatal issue more often took place on the sixth or seventh day. The record goes on to state

Many women sickened and it was rare for a pregnant woman to survive if attacked. The robust, young and healthy died first. Of those of tender age attacked few died as compared with the adults and aged. God spared the young and innocent, but not the sinful elders.

Indians and Spaniards were both attacked. The description gives all the characteristics of yellow fever among a non-immune population. Strangely enough the writer does not speak of jaundice,

unless *páldos* covers the yellowness of the fever and the pallor due to the anæmia. It was noted that relapses and second attacks did not occur, though the epidemic lasted for two years.

History affords us a clue to the origin of this outbreak. During 1648 piracy and buccaneering on the part of the French, Dutch and English were prevalent, Campeche was sacked in 1633, 1644 and again the following year. In April 1648 vessels sailed between Vera Cruz and Campeche. Ligon noted that in 1647 in Barbados there was "the Plague or a disease as killing as plague." St Christopher's was another resort of the buccaneers and according to Père du Tertre, the historian of Guadeloupe and Martinique, there was a severe epidemic of yellow fever in St Christopher's in 1648 which resulted in the deaths of nearly one-third of the inhabitants, and from there infection was conveyed, it is said, to Guadeloupe by the vessel *Le Bœuf*.

As for Haiti, some authorities, among them Moreau de Jonnés, believed that yellow fever was endemic there before 1492 when the Spaniards first arrived, others, among them Finlay and Béranger-Féraud, hold that it was introduced three years after by Caribs from the Lesser Antilles or the mainland. We may ask why, since commerce was carried on between them before that date, infection, if present in the Antilles or on the mainland, had not been introduced, from one to the other earlier. The sickness mentioned by Columbus as occurring in 1493 was certainly not yellow fever, that of two years later resembles malaria rather than yellow fever, but the fatality rate was very high. According to Las Casas, of 1500 who came in 1493 with Columbus, 80 per cent had perished by 1502, only 300 remaining. According to Del Monte, the original number was 1300 (and he is usually more accurate than Las Casas), if so, the percentage loss would be 77. We may utter a word of warning here. It is a curious fact that in the early Spanish writings on epidemics in the Americas we find in a great majority—in nearly all, we may say—the record that the outbreak "carried off one-third of the people." In the accounts of the expeditions of Ojeda and Kimesa, the deaths which occurred were due not to any disease resembling yellow fever, but to malaria, starvation, injuries inflicted by the natives, arrow poison, poisonous foods, and so on.

Balboa and Darien, in the early years of the sixteenth century, were quite prosperous, the inhabitants were on friendly terms with the Indians, and immigrants came especially from Hispaniola, nevertheless there was no sickness construable as yellow fever. In June 1514 Pedro Arias de Avila (Pedrarias Davila, as he is

sometimes called) came from Spain and superseded Balboa. He radically changed the policy of his predecessor and instead of living amicably with the natives he and his troops raided them for gold and slaves. Food was less easily obtained and what they had they wasted, sickness supervened and many fled to Jamaica, Cuba and other islands. The sickness is spoken of as *modorra* which, as already stated, means drowsiness or stupor. It is recorded that deaths numbered fifteen to twenty a day and in one month 700 died of "hunger and *modorra*."

In Guadeloupe there was an important and widespread epidemic in 1635, known as *coup de barre*. This was preceded by a famine (*disette*) which must have been very severe, since it is recorded that the people ate their dogs and later even turned cannibal. *Coup de barre* or 'blow with a stick' was associated with violent headache, throbbing vessels, dyspnoea, pain in the legs, as of bruises from cudgelling—hence the name. It appears to have been no new disease, it is said, because the natives had a name for it—*reponlicáatina*. This, however, is an argument of doubtful validity, for the same word is held also to mean 'a blow from a stick' and is the translation of *coup de barre* and was more probably just an adaptation by the Carib natives of the French term. The mortality was low and the disease is not likely to have been yellow fever therefore. Though a mere conjecture, one might venture to suggest that it was dengue, a disease associated with severe bone and joint pains, hence its synonyms of dandy fever, breakbone fever. Incidentally, infection is transmitted by the same mosquito as carries the yellow fever virus. "It seems strange," writes Carter, "that this *coup de barre* has been so generally accepted as certainly yellow fever, especially so when that opinion has generally been based solely on the account by Du Tertre."

A very trustworthy criterion as to whether a locality has not for a long time at least suffered from yellow fever was, prior to the recently introduced protection immunity test, the aptitude of the population to contract the infection when introduced. Judged by such a standard Cuba was free from yellow fever for the first 138 years of its being occupied, outbreaks of sickness reported during that time indicate smallpox. But in 1649 we see a totally different picture. An outbreak occurred and spread all over the island. It is recorded that there perished "a third part" of the garrison and civilians in Havana and an even larger proportion of the crews and passengers in vessels anchored there. Another noteworthy point is that shortly before there was a large

influx of buccaneers, just as there had been at Campeche preceding the outbreak there. That this outbreak of 1649 was yellow fever rests on fairly sound evidence—the chief points are that the disease rapidly progressed to death in a few days, that the fatality rate was high, that it prevailed on the vessels in the harbour and in the town of Havana and later spread to other towns, invading with equally fatal effects Santiago and Bayamo, that in the preceding year yellow fever was present in Yucatán and the French Antilles with which there was direct communication by Spanish vessels and by the buccaneers.

After 1655 the disease seems to have disappeared from Cuba for more than a century. In 1761 infection was again introduced, this time from Vera Cruz, by prisoners sent over to help in building *cabañas* (huts, dwellings). In 1762 there was an expedition of English and colonial Americans to get possession of the island, but after a few months so great was the loss that the project was abandoned. From that time the infection was permanently endemic there till the beginning of the present century when Surgeon-General Gorgas took on the task of its eradication with such signal success (see later). In the decade 1884–94 on an average there were 210 deaths per annum from yellow fever among the civilians—Spaniards, Cubans, foreigners—and almost entirely the immigrant part of the population. The Spanish Army, in its efforts to put down the Cuban insurrection in the 'nineties, found yellow fever a more formidable foe than the poorly equipped 'insurrectos,' and the American Army lost many before Santiago from yellow fever, as they had done half a century earlier before Vera Cruz. Many, not included as cases of yellow fever, suffered from "fever of acclimatization", these were, a certain proportion of them at least, cases of mild or non-fatal yellow fever, escaping recognition.

Similar disappearance of the disease for long periods after extensive outbreaks has been observed elsewhere, as in Olinda, adjacent to Recife, after 1686, and in Bahia the same year. It prevailed there for some years and did not reappear till it was reintroduced in 1849 from New Orleans or, perhaps, Havana.

In 1686–90 it prevailed in Martinique, infection having been brought, it was believed, by a French warship, the *Orriflamme*, from Bangkok. From Martinique it spread to other West Indian Islands and, from its reputed source, went by the name of *maladie de Siam*, though yellow fever is totally foreign to and quite unknown in Siam. One report states that the vessel was driven out of its course by storms and called at a Brazilian port on

the way, probably bringing the infection on from there - Over a hundred persons died of *Typhus miasmaticus ataxicus putride jaune*, the unwieldy name by which yellow fever was known to the French

Hirsch in his *Handbook of Geographical and Historical Pathology* notes 148 epidemics in the West Indies North and Central America, and the Mexican Gulf coast of South America in the 234 years between 1645 and 1879, and that there was some outbreak almost every year from the beginning of the eighteenth century. A list of all the outbreaks which we have been able to collect is given later

On the mainland of South America (we quote Hirsch) yellow fever has become widely diffused only since 1860. Prior to 1830 there had been only two outbreaks diagnosed with certainty as yellow fever, both of them at Guayaquil, one in 1740, the other in 1842, and in both cases the infection was believed to have been imported, in the second from New Orleans. Peru was infected in 1854 from Brazil, by the agency of emigrants travelling by a German vessel, Callao was first infected, then Lima, and the disease persisted for the ensuing fifteen years or more

Yellow fever has occurred in Europe, as is seen from a perusal of the list of outbreaks given later (see pp 323-50), and the epidemic at Cadiz in 1730 is particularly noteworthy on account of the havoc it wrought. Into Europe infection was, of course, imported and was almost limited to the south-west coast of the Iberian peninsula and to Majorca. There are several records of ships arriving at European and British ports with yellow fever on board, a few may be enumerated without details at present. Thus, it was brought to Brest in 1802, 1839 and 1856, to St Nazaire in 1865, to Swansea in 1843, 1851, 1864 and 1865, and to Southampton in 1852, 1866 and 1867. At Swansea in 1865 not only were members of the ship's company, the *Hecla* from Cuba, infected but customs officers and the ship's labourers were attacked. On her arrival on 9th September, 1865, one of the crew was dying, two others were convalescing. From 15th September to 4th October twenty persons of the town in definite local relation with the ship were attacked and three of the crew of a small vessel which had been lying alongside the *Hecla*. The latter must, it seems, have brought infected *Aedes* also

The St Nazaire outbreak was more interesting and more serious. The history of this is as follows. On or about 13th June, 1865, the *Anne Marie*, a wooden vessel, left Havana with a cargo of sugar, yellow fever was epidemic at Havana at the

time Between the 2nd and 12th July members of the crew were attacked, and on the 25th the ship arrived at St Nazaire. The last death from yellow fever had taken place on 5th July, twenty days before, and the last case of infection on the 12th July, or thirteen days before, the vessel was, therefore, granted free pratique. On the 5th or 6th August many of the labourers who had been unloading her fell ill with the fever. On 1st August the *Chastan*, which had been lying alongside the *Anne Marie* but had moved on to Indret, had her first case and by 5th August the whole crew of five had been attacked. When the *Chastan* sailed, the *Dardanelles* took her place and the only person left on board, a boy, was attacked. During the few days that the *Chastan* lay by the *Anne Marie*, the *Cormoran* had taken cargo from her and had then proceeded to Lorient. After arrival there two of her crew went down with the fever. Another ship, whose name is not known, which had been near the *Anne Marie* in St Nazaire also had two men attacked. Yet more, two lighters from Indret which had been by the *Anne Marie* for two days furnished seven or eight suspicious cases, recorded as "a kind of half-yellow fever" [whatever that may be] and another vessel, the *Arequipa*, a steamer, the seventh to come in connection with the *Anne Marie*, lying near her for some days, had a case on 5th August which was followed by several others.

An explanation had to be found for such an extraordinary series of cases, all clearly originating from the *Anne Marie* and the plausible suggestion was made that

the organism [vaguely] had grown readily when once planted in the moist hold and in the unventilated apartments of the ship, so that certain portions of the wooden surface would be found, if they could be examined with a strong microscope, to be covered with colonies of many thousands or millions of microbes, and articles of merchandise might similarly nourish plentiful crops in a close and hot atmosphere. At any rate the results are consistent with such a view.

This method of argument savours somewhat of that of the school-boy who works out a problem by first looking out the answer.

The Pensacola outbreak in 1874 was, it may be incidentally mentioned here, similarly the result of importation by the Spanish barque *Virtuoso*, from Havana.

This is a convenient place to mention an instance of ship-borne yellow fever in quite modern times. A vessel, the *Sea Rambler*, was at Kaolakh and Zighinchor for a week from 31st July to 7th August, 1936, taking on cargo, and two days later left Dakar to return to the Tyne. While at Zighinchor the crew

had found the heat very oppressive and mosquitoes more than usually troublesome. On the 13th August, that is four days after leaving Dakar and a fortnight after arrival to take on cargo, one of the crew fell ill with high fever and rapid pulse, the next day another fell ill. By the 17th a steward and three of the crew were sick and the captain decided to call in at Madeira for medical advice. During the ensuing two days four more men were taken ill. On arrival at Madeira on the 20th three of the sick were taken to hospital at Funchal, a diagnosis of intestinal toxæmia resulting from some sort of food-poisoning being made. The same day the one who had fallen ill on the 14th died and the captain and yet another sailor were attacked with fever. Eight days later the vessel left for Dunquerque, the crew now consisting half of new hands. She arrived at Dunquerque on the 6th September where she remained discharging cargo for five days, left there on the 11th and reached the Tyne on the 12th.

Altogether out of a crew of twenty-four there were fourteen attacked and seven died. Five were kept in hospital at Madeira, two were taken ill but remained on the ship and returned to duty. On arriving at their home port the sera were obtained from ten of the crew and subjected to the mouse protection test (see later, p 411). Eight samples from persons who had presented no symptoms gave negative results, the other two were positive. These were from the men who had been ill but had recovered and gone on duty again. Four samples were obtained from the patients admitted to hospital in Funchal and all gave positive findings. In neither the *Hecla* nor the *Sea Rambler* cases did the disease spread beyond the close environs of the ship because the *Aedes* present must have been similarly limited.

The geographical limits of yellow fever are, in the Western hemisphere, 34° 54' South latitude (Monte Video) and 44° 39' North (Halifax), in the Eastern hemisphere 8° 48' South latitude (Ascension) and 51° 37' North (Swansea). The northern extent of occurrence in epidemic form is, in the Western hemisphere 43° 4' (Portsmouth, New Hampshire) and in the Eastern 43° 34' (Leghorn). We can, therefore, state in general terms that yellow fever is definitely a 'tropical disease,' that is a disease of warm places and warm seasons. It is, however, not present in all parts of a country in which it is endemic, but only in certain districts, for example it often is absent at higher altitudes in an otherwise 'tropical' country. In West Africa, the West Indies, the coasts of Mexico, places where the climate is hot and moist, yellow fever may be present all the year, but permanent only where the mean

winter temperature is at least 70° F ; at higher altitudes it will be epidemic only in the hot season

Thus, yellow fever outbreaks have often been reported in the United States (some of them are mentioned in the list of epidemics, pp 323-50), notably in New Orleans, Philadelphia, New York, Charleston, Mobile, Baltimore, New Haven and elsewhere, but it cannot be said to have been really endemic there, the virus is destroyed, or the activity of the mosquito checked by the cold of an American winter in, for example, Charleston, Baltimore, Philadelphia and New York, but not at Gulf ports such as Galveston, New Orleans, Mobile, Pensacola and Key West It is, therefore, mostly a summer plague, the mortality has at times been very high Thus, in Philadelphia in 1793 there were some 17,000 cases and over 5,000 deaths, a veritable decimation of the entire population, rich and poor were both attacked, no age or colour was exempt, and the clean suffered as well as the filthy For the time being an end was put to community life, all who could get away left the city, banks were closed, factories shut down, newspapers were no longer published, churches had no congregations, thousands of workers had no employment—in short, the condition of things was very like those of London in the plague year, 1665, on a smaller scale It was said that family ties were strained and severed, husbands abandoned their sick wives, wives husbands, and parents their children The outbreak ceased when the cold, frosty weather set in, as mysteriously as it had begun The fact was noted that some who constantly associated with the sick did not contract the infection while many who never, so far as they knew, had been near a patient fell victims Dr Rush noted that “moschetoes were very plentiful” about Philadelphia in 1793, and Webster describing the New York outbreak two years later said “mosquitoes were never before known by the oldest inhabitants to have been so numerous”

In Galveston outbreaks were common after 1839 and at times were accompanied by heavy mortality, in 1867 there were 1150 deaths from yellow fever among a population of 22,000 There can be no doubt that the infection was endemic, but there was frequent or continuous introduction of fresh virus from outside communication Similarly, outbreaks were frequent in New Orleans from 1822 to 1860, after which there seems to have been a lull, but in 1878 a serious epidemic caused 4046 deaths

We see then that in non-tropical places yellow fever prevails at, or mostly at, warmer seasons, in Rio de Janeiro in the course of twenty years 8554 fatal cases were recorded, of these 89 per

cent occurred in the first half of the year. In cooler places the yellow fever season is the summer, perhaps passing on into early autumn. For *rise of the fever* a temperature of 80° F seems to be necessary, but having become established it will continue though the temperature falls well below this, because *Aedes ægypti* is a domestic mosquito and will live, especially in the shelter of houses, though the temperature is low. In fact, when imported into Spain it has survived the winter and given rise to a fresh epidemic in the ensuing hot weather period. When present on board ship on the Gulf Coast it may persist—in fact, it has repeatedly persisted—into temperate latitudes, then remained in abeyance while the ship was at Newfoundland, reappearing as the vessel returned south.

Let us take, for example, a year within the memory of all, 1913, the year preceding the outbreak of the Great War, and note the places where the disease was reported. In *West Africa* Nigeria (29 cases in Lagos), Togoland, Gold Coast Colony, Portuguese Guinea, Senegal, French Congo. In *South and Central America* Brazil, Manaos (39 deaths), Para, Ceará, Pernambuco, Bahia, Rio de Janeiro. In *Venezuela* Caracas. In *Colombia*. In *Peru* Iquitos. In *Ecuador* Guayaquil (221 cases, 123 deaths), Milagro (66 cases, 34 deaths), Naranjito (38 cases, 24 deaths), Duran (18 cases, 9 deaths), Agua Piedra, Bucay, Bababoyo, Yaguachi. In *Mexico* Campeche. In the *West Indies* Havana (by steamship from Manaos and Campeche, nowhere else in Cuba), in Trinidad (10 cases in Brighton).

Opportunity may be taken here to correct an erroneous report. In the United States Public Health Report for December 1913, twenty-eight cases of yellow fever were mentioned as having occurred in East Africa, twenty-five of them at Mombasa, Kenya Colony. A month later, after three appearances of this report, there was a note stating that "plague in British East Africa had been erroneously entered as yellow fever and this was repeated later." Nevertheless in a Quarantine Map of the World the original error was repeated. Prominence is given here to this, because, if it once gain entrance into the textbooks, it is probable that the correction will never overtake the error. Yellow fever has never been reported from British East Africa. This is not merely of academic import. The diagnosis, as we shall see shortly, in early days was not always clear cut and it may be thought that 'doubtful' cases occurred in Mombasa in 1913, if the report is quoted, secondly, recent research by means of the protection test has shown that the disease has occurred unrecognized in

places where its existence was totally unexpected (see later), and these may be put down as cases of the disease arising from some cryptic source of infection. The United States Public Health Reports are so valuable for epidemiologists and have so much weight that the authorities at Washington would be among the first to have the doubt cleared away.

2 DIAGNOSIS IN EARLY DAYS GEOGRAPHICAL DISTRIBUTION

We may leave this aspect of the question and pass on to that of uncertainty of diagnosis in the earlier days.

William Fergusson describes yellow fever under the name of *Hæmogastric Pestilence* in his account of an expedition to Santo Domingo (Haiti) in 1796 and he shows clearly its prevalence at low levels and absence at high altitudes.

Our headquarters were the town and its adjunct Brizoton, as pestiferous as any in the world, [one cannot help wondering, for there is no statement on the point, why, if this were so, it was selected for headquarters] and here we had constant yellow fever in all its fury. At the distance of a mile or two, on the ascent up the country, stood our first post of Torgeau, where the yellow fever appeared to break off into a milder type of remittent. Higher up was the post of Grenier, where concentrated remittent was rare, and milder intermittent with dysentery prevailed, and higher still was Fournier, where remittent was unknown, intermittent uncommon, but phagedænic ulcers so frequent as to constitute a most formidable type of disease, and higher still were the mountains above L'Arkahaye, of greater elevation than any of them, far off, but within sight, low down in what was called the bight of Lergane, a British detachment had always enjoyed absolute European health, only it might be called better, because the climate was more equable than in higher latitudes.

The separate regions or zones of intertropical [country] were here mapped out to our view. Taking Port au Prince for our point of departure, we could pass from one station to the other and with a thermometer might have accurately noted the locale of disease according to the descending scale, without asking a question among the troops who held the posts. It was just as impossible, or more so [*sic*] to carry yellow fever up the hill to a post in sight as it would have been to escape, had they been brought down and located amidst the swamps of Port au Prince.

More will be said shortly on the confusion between yellow fever and forms of malaria, for the author of the above statement was not alone in mixing up yellow fever with remittent and intermittent, and in thinking that one might pass into the other, or replace one another, and have a common cause. He did note, however, that the area of yellow fever might be limited, and he advised the leaving of a place where it was prevalent and not returning

to it until the disease had disappeared and been absent for some time

While the coloured population and acclimatized Europeans suffer only from remittents or from the very milder forms of yellow fever [perhaps he implied bilious remittent fever] the unacclimatized European is everywhere and at all times the victim of the most virulent and fatal form of this epidemic

He noted also "a first attack of yellow fever gives a certain degree of immunity from a second, proving so far self-prophylactic" The author qualified his statement, probably, one imagines, because he saw a patient who had had yellow fever suffer from bilious remittent fever, or *vice versa* The disease was very fatal in San Domingo and other West Indian islands in 1795 and the following years Among the European troops, it is said, in a little more than four years nearly 700 commissioned British officers and 30,000 soldiers died of it, and "one of the finest armies of France perished, at least for all purposes of an army, within the year" [at San Domingo], and in the West Indies in 1794-5 "there died in the course of a few months not less than 6000 men"

To save our having to return later to the question of yellow fever in the West Indies in this section a few words may be said now as to outbreaks of the disease in this part of the world The West Indies have been called the 'cradle of fevers' and one of these, yellow fever, was at one time thought to be lying in wait for every newcomer, who was expected to go through an attack before becoming acclimatized

In the eighteenth and early nineteenth centuries types of fever were not as a rule differentiated in the official returns, so 'deaths from fever' included those from malaria, yellow fever and probably enteric Here are some of the returns showing how deadly the climate was supposed to be In 1741, of 12,000 men under Admiral Vernon and General Whitworth at Carthage 8431 died, in 1762 at Havana 3000 sailors and 5000 soldiers were down with fever within a month of landing, under Count Albemarle In the twenty years 1817-36 the annual mortality per thousand among white troops in *Jamaica* was 150.7 at Montego Bay, now one of the healthiest parts of the island, 141.1 at Spanish Town (St Iago de la Vega, then the capital), 121.0 at Up-Park Camp, Kingston, while among the black troops the ratio was only ten *per mille* In 1817 at *Dominica* 29 per cent of the white troops died of fever, and in the following year in *Trinidad* 30 per cent At *Tobago* in 1818 13 per cent, but two years later

the morbidity was appalling and the fatality rate was said to be 80 per cent. The next year it dropped to 25 per cent.

Barbados in this respect has an interest because it was free from intermittent fevers—malaria was absent. The first knowledge we have of yellow fever there is from Ligon's History and it was supposed to have invaded the island for the first time in 1647. In 1691, under the name of Kendal's disease, it was re-introduced from Pernambuco. Between 1815 and 1846 it was continually present and the percentage of admissions to military hospitals ranged between 5.2 (in 1836) and 87.8 (in 1841). After 1881 there was no record of the disease there until November 1907 when it appeared in Bridgetown and in the succeeding three months spread to other parishes. One hundred cases were recorded, and as evidence that infection had been introduced afresh it is to be noted that 54 out of 86 black residents were attacked. Doubtless many early cases were missed or not reported, partly because after so long an interval it was not looked for, partly owing to obstruction by the press which vehemently expressed disbelief and intimidated so far as it could anyone, medical or lay, who ventured to make a diagnosis of yellow fever. When the nature of the disease could no longer be concealed there was much speculation as to the source of infection. Some thought it might have been brought from Martinique where a serious epidemic prevailed from June 1908 (if Barbados was infected thence, it must have been brought by earlier cases as the outbreak in Barbados began at the end of 1907), or from Surinam, Venezuela or St. Vincent, in all of which yellow fever was present, but in 1908 and the remark above applies here also. The most likely source was Trinidad. Cases were certainly occurring there in January 1907 and therefore probably some at the end of 1906. The United States ship *Atrato* on 10th August landed a stowaway from Trinidad, suffering from yellow fever. Even earlier, on 7th December, 1906, a case was landed by S.S. *Marantence* from Para, and the journey from Para to Barbados occupies only 4½–9 days. In Barbados the drinking water was kept in barrels or other receptacles in the kitchens of the dwellings and the *Aedes* is largely a domestic mosquito.

In 1919 there was an outbreak of jaundice accompanied by fever which raised a good deal of suspicion. Guiteras was deputed to investigate it and he decided that though in some respects it resembled yellow fever this disease was ruled out on the following grounds. It was confined to the poorer classes of blacks, nine out of ten fatal cases were in natives, though the liver was dark

and congested in some and 'boxwood-like' in others, the histological findings were not those regarded as characteristic of yellow fever. The stomach contained black grumous fluid, another point in favour. On the other hand the temperature was not like that of yellow fever, the duration of disease (average 6.8 days) was longer than that of fatal yellow fever (6.4), and recovering cases were also of longer duration, 13.6 as against 7.4 days.

In *Nassau*, or New Providence as it was called, the capital of the Bahamas, there is recorded that soon after the erection of Fort Charlotte at the end of the eighteenth century "the whole of the 47th regiment, men, women and children, were swept off by yellow fever in a few weeks." This must be an exaggeration, but doubtless the fatality was very great. In 1802, of 300 men of the 7th Fusiliers 220 died, and in the following year 250 out of the same total. In 1818 forty deaths occurred from this disease, in the 15th Regiment in six months. With such a reputation we cannot be surprised to hear that Fort Charlotte came to be called 'The Abode of Death'.

British Guiana has a chequered history as regards yellow fever. It is interesting to note that Beauperthuy, the first to suggest mosquito transmission of yellow fever, settled in this colony. In 1820 the mortality from the disease among the troops was recorded as 16 per cent and in the following year 14 per cent. In 1840 there were

many hundred acres of jungle forming a well-sheltered swamp and a marsh of 250 acres and during each spring the sea covered the surface of the marsh. Near the public roads were small gullies, communicating apparently with the jungle and containing frothy, putrid-looking water. Within the trenches aquatic larvæ abounded and over them clouds of mosquitoes and sandflies.

The military hospital was situated to leeward of this marsh and it was in 1840 that a severe epidemic took place and 69 per cent of the white troops died in a few months.

The last recorded outbreak in British Guiana occurred in 1881 and there was no case after 1888 till half a century had elapsed. Then, in 1938, British Guiana appeared once again in the list of yellow-fever countries. Two Indians in the Rupununi district were attacked and five out of forty-six samples of blood from natives in the region gave a positive reaction to the mouse-protection test. This proportion is comparable with results recently recorded from Dutch Guiana.

The cause of the disappearance of the disease for so long is uncertain. In many places it can be ascribed to the installation

of a piped water-supply and abolition of domestic storage receptacles, but not in this instance. A partial supply was, it is true, introduced in the eighteen-forties, but rain-water was still the chief source and it was stored in vats or other receptacles. We can only put its absence down to strict quarantine and supervision and better housing and improved sanitation in general.

In Surinam, *Dutch Guiana*, epidemics were recorded in 1902 and 1908. Both of these outbreaks coincided with the advent of many susceptibles, and it was these who were mainly attacked and fatal cases occurred only among them. Europeans who had sojourned for some years in the country were either immune or suffered from it in an abortive form. Tests made with sera from the inhabitants showed several positive from individuals between eight and twenty-five years of age.

Grenada became re-infected in 1793 after a considerable interval of freedom. In that year a ship, *Hankey*, having sailed from England to Sierra Leone and to Bulam, proceeded to Grenada with the disease on board. It spread to Jamaica, San Domingo and to Philadelphia where in the course of a few months it caused the deaths of 4000 persons. The synonym *Bulam Fever* arose from the fact that the vessel had come thence to Grenada. Grenada has suffered less than most of these islands from yellow fever, an outbreak was recorded in 1804, but no details are available. In 1817 the death-rate among the troops was 8.2 per cent and the following year 21 per cent. In 1881 there were a few cases. In 1837 a pipe-borne water-supply was introduced, but on a limited scale, there were only four standpipes and the houses were not supplied directly. In 1879 the supply was greatly augmented and we are probably correct in regarding this as the main cause of the disappearance of the disease. In 1907 two cases were discovered, imported from Trinidad, but they were promptly dealt with and no secondary infections arose.

Records as regards *St Vincent* are meagre, perhaps there have been few cases to note. It was imported there from Barbados in 1909 (but, as we saw above, Barbados believed that its outbreak of that year had arisen possibly from importation from *St Vincent*).

St Lucia has suffered repeatedly. After Sir Ralph Abercromby's attack on the Morne in 1796 a garrison of 4000 men was left under the command of Sir John Moore in June. In five months yellow fever had reduced the numbers to 1000 fit for duty, and 1500 were sick (Fortescue's *History of the British Army*). The campaign lasted from 1793-6 and resulted in 80,000

soldiers being lost to the service, half that number having died, in 1795 among a force of 1400 there were no less than 600 sick and on the very day when the English were leaving St Lucia one officer and seven men died. The deaths exceeded the total loss in Wellington's army from all causes—deaths, discharges, desertions—from the beginning to the end of the Peninsular War.

Years notable for prevalence and fatality of this disease in St Lucia are 1818 (with 14.5 per cent fatal), 1822, 1824 (21 per cent fatality), 1827 (the same) and 1832 (30.8 per cent). In 1839 there was an outbreak among the troops at Morne Fortuné, of 134 persons 93 were attacked and 20 died. In 1848 a piped water-supply was constructed, but many householders retained their old receptacles, barrels, olive jars, and cisterns and tanks were not abolished. Some cases were seen in 1901, the cause assigned being "excavations for railway construction," which means, of course, pools for mosquito breeding.

Trinidad and *Tobago* have already been mentioned. Both in the early and late years of the nineteenth century the disease occurred there and in the former at times proved a veritable scourge. In 1818, as we saw, the mortality among the troops in Trinidad due to yellow fever was 30 per cent, between 1820 and 1825 it fell to a tenth of this, but in 1828 was up again to 13 per cent, indicating that the infection had then become endemic. In Tobago in the years 1818–21 the fatality among the white troops was 13, 18, 80 and 25 per cent respectively.

In 1851 a piped water-supply was introduced, better drainage was installed and the building construction improved. Anthony Trollope saw yellow fever when he was in Trinidad on his tour of the West Indies in 1870. He noted that it had been working dreadful havoc, chiefly among the white soldiers. The barracks were near the shore and the locality, St James, was notoriously unhealthy. The fatality was high. Improvement set in when the troops were removed to tents erected in the savannah at a distance from the shore.

From its position Trinidad is much exposed to imported infection. Cases of yellow fever were reported in 1889, 1891, 1894, and a small outbreak in 1907. Between January and March there were five cases, all new arrivals, all were seriously ill and four died. We are almost justified in inferring that there were unrecognized cases present in Trinidad about this time. By August there had been 38 attacked, and by the following March 47, of whom 28 died. Investigation as to the original source implicated Venezuela, yellow fever is endemic there and Trinidad

lies close to it, so that it is not unlikely even that Trinidad itself was at that time an endemic centre

On yellow fever in the *Bermudas* Trollope makes the following interesting remark Bermuda has

the most trying climate that I had encountered They have had the yellow fever there twice within the last eight years and on both occasions it was very fatal Singularly enough on its latter coming the natives suffered much more than strangers

This goes to show that the disease was not endemic there, the greater prevalence among natives, if it really was so, may have been due to their living more closely together and unprotected from mosquitoes

Lastly, a reference or two to the *French West Indies* Père Labat speaks of an outbreak in Martinique in 1649, in 1735 a severe epidemic occurred in St Pierre, Guadeloupe Definite outbreaks are recorded in 1850-3, 1855-7, 1887-8, 1895 and 1908-09, and in the intervening years suspicious cases were observed The one last mentioned seems to have had a local origin, starting in Fort-de-France and spreading radially all over the island Among the natives there were many cases of mild 'inflammatory fever,' the nature of which was overlooked, and others were not discovered and soon the disease spread to the recently arrived non-immunes In the twelve months, February 1908-09, there were 206 cases, but this number does not include many cases of quite mild fever amongst children, another estimate gives close upon a thousand cases in all

Turning now to *Africa* we find that it is not possible to trace out the medical histories of West African colonies, because there are no reliable records of the early days G M Findlay and T H Davey in an article on *Yellow Fever in the Gambia* have delved into the early history and demonstrated the colony's reputed unhealthiness For much of the information which follows we are indebted to their article (*Trans Roy Soc Trop Med and Hyg*, v, 29, 667, v, 30, 151)

Gambia was first visited in 1455 by Alvise da Cadamosto, a Portuguese, in 1456 he proceeded some sixty miles up the river to a place called Battimansa when fever broke out and in eleven days attacked so many of his crew that he decided to return to the river-mouth In the next two years a similar experience befell Diego Gomes who went with two caravels up the river, fever attacked the crews and several men died We know little more till the year of the Spanish Armada when we find that a

trading-post had been established (1588) but did not succeed. Thirty years later another company was formed and set out in the *Catherine*, under Richard Thompson, they met with a hostile reception and most of the crew were massacred. Next year another ship was equipped but "arrived at an improper season" and most of the crew died of sickness. Forty-five years later, in 1664, the Royal African Company was established on James Island and during the ensuing half-century reports on the unhealthiness of the Gambia were frequent. "These musketoes are the greatest plagues to one's person of any other vermin on the River. The musketoes mind neither wind nor anything else but are always plaguing one, especially at night." Lind noted that treatment by quinine (he is quoting Martin, a ship's surgeon out there) did not put an end to fevers and that mortality was great, but that the desired result was attained by making the vessels draw out and anchor half a league from the shore. Lind also gives an account of an outbreak on a ship in 1768. Members of the crew of the *Merlin* spent six days in the River Gambia, in wooding and watering. Two days after putting to sea several of those who had been so employed fell sick and more than a week later those attending them were attacked "leaving no doubt of the disease being infectious" (Reference to the original log of the *Merlin* reveals discrepancies in dates). An account somewhat similar to, but more substantially detailed than, this is found of another vessel, H M sloop *Weasel*, the following year. This ship arrived at the Gambia on 28th July, several of the crew went ashore and the officers were shooting on 7th August, she sailed down the river again next day. Single cases of fever developed in the first fortnight of August and in the succeeding fortnight thirty-three cases of remittent fever were treated among a crew of ninety. On the 27th the ship was 'smoked' and one further case developed on 2nd September.

There must be considerable doubt as to this being yellow fever. An eruption about the mouth is mentioned, vomiting was a common symptom, some showed purple blotches and one had bleeding from nose and mouth and hæmaturia. There is no mention of black vomit, of ten fatal cases three died on the seventh, two each on the eighth and ninth, and one each on the tenth, twelfth and fourteenth days, and one who recovered had a crisis on the eighteenth day of illness. In some there was jaundice on the seventh day.

Ten years later cases were reported in the Gambia resembling those described in 1780 by Schotte in Senegal. Bathurst was

founded in 1816, the population consisting of a few European traders, but mainly of freed slaves. In 1825 an outbreak of fever occurred, yellow fever without much doubt, and caused the death of seventy-four out of a detachment of 108, but in 1837 occurred the first outbreak definitely diagnosed and described as yellow fever, the infection was believed to have been introduced from Sierra Leone. The outbreak is described fully in Sir William Pym's *Observations upon Bulam, Vomito-Negro or Yellow Fever*, published in 1848. The *Curlew* left Sierra Leone during an epidemic there in May 1837 and reached Bathurst on 4th June, several of her crew had died and others were dying. Half the Europeans in Bathurst fell victims. Five of them, with the Colonial Secretary, left for Senegal, but all died there and the inhabitants of Gorée became infected, whether from these Europeans or independently cannot be stated with certainty.

In 1872 the prevailing diseases in Bathurst were said to be yellow fever and smallpox, and this town had become an endemic centre, and from that time deaths of Europeans were occasionally recorded as due to "bilious hæmaturic fever," a synonym of yellow fever. A more extensive outbreak occurred in 1900 and this date is to be remembered as it is the first there in which mosquitoes were specifically incriminated as vectors, all the cases except one occurred in the street most infested with mosquitoes. There was no further outbreak for eleven years, when in 1911 four cases occurred in May, three of them fatal, six in July, five fatal, and one fatal case in November—eleven in all and nine of them fatal. This outbreak is noteworthy for the temporary disappearance of the disease in May to reappear in July, disappearing again at the beginning of August and reappearing in November for ten days. All four of the May patients (and a fifth possible one) were friends and often associated together in the Royal Engineers' quarters, and it is thought that the mosquitoes in the quarters became infected from a mild case in a native soldier. Besides the six mentioned in July there were several other suspicious cases, unconfirmed because of insufficient evidence. In addition to the fatal case recorded in November, after three months without any being reported, a friend of this patient also became ill and died with symptoms suspicious of yellow fever. The source of infection in this patient was not detected.

Since then there have been occasional cases, in some years as in 1922 and 1928 four or five were recorded, but in October 1934 there was a more serious outbreak. Little need be said about it here, it will be referred to again later in connection with

recent work on the disease and *ex post facto* diagnosis by means of the protection test The population at the last census (1931) was returned as 14,370 (in 1840 it was 2825 Africans and 36 whites) So far as vital statistics can be relied upon the increase was due mostly to immigration, for only in 1909 had births exceeded deaths On 6th August an African woman was admitted to hospital suffering from fever, the nature of which was not diagnosed, it was not malaria, at all events no parasites were found Her blood when examined five months later showed that she had at one time suffered from yellow fever, but that may have been before the 1934 attack In the following months deaths were rather more numerous than in the same months in previous years, but during the last quarter of the year the deaths showed a distinct increase, especially among adults and the distribution of cases resembled that of the 1911 outbreak

Sierra Leone has been regarded by many as the home of yellow fever, in the nineteenth century the disease was common there, but did not attack the natives to an extent recognizable clinically, in other words it was endemic there In 1826, out of a garrison of 535 there died 115 between 14th June and 24th August In 1837 H M S *Curlew* stayed at Freetown for a week and thence went on to the Gambia and, as stated above, it was believed that by this means the Gambia became infected That this was quite possible finds further confirmation in the following record in which the sequence of events is altogether typical

On the 2nd November, 1844, H M S *Eclair* left Plymouth for Sierra Leone and arrived on 22nd February, 1845 For a time the general health of the ship's company was good and no disease was recorded among the crew For the first three weeks (till 16th March) they were employed in exploring the creeks and at times they spent the night on shore Eighteen days later, on 3rd April, the first case of fever occurred, and between that date and the 15th June there were twelve, seven ending fatally and two fatal cases occurred among those who had remained on board On 4th July the ship returned to Sierra Leone with the last patient convalescing For the next few weeks the men were employed in surveying the stores of another ship, the *Albert*, and in clearing out her hold The men during this time were permitted to go ashore The *Eclair* then sailed for the Gambia and on the journey thither fourteen of the men were attacked with fever and seven of them died It is noted that several were jaundiced and some suffered with black vomit Between the 15th and 17th August two more deaths occurred and the *Eclair*, after taking in coal at

Gorée, went on to Boa Vista, arriving on 21st August. Two other cases of fever occurred on board but were regarded as "common African fever" and pratique was therefore granted. In the next nine days sixteen more of the crew were attacked and five died and in the ensuing fortnight more were attacked and twenty-five died, later, fever broke out at Boa Vista. In his summary of this outbreak Dr M'Williams states

1 Boa Vista was healthy till the *Eclair* arrived with yellow fever on board

2 The disease broke out "within a reasonable period" afterwards among the inhabitants

3 Distant villages remained free for long periods till the arrival of infected persons and radiation of the disease in every district from infected foci

The *Gold Coast* was the scene of several outbreaks early in the nineteenth century, about the middle of the century the garrison was withdrawn, there was absence of the usual influx of non-immunes and consequently a lull in the prevalence of the disease. Later, however, as commerce developed and new centres of activity were established the disease broke out again. By no means infrequently, and particularly at the beginning of an outbreak, medical officers refrained from giving the more serious diagnosis for fear of setting up alarm should their suspicion prove unfounded. Though, moreover, they have discussed the possibility and even reported cases as probable yellow fever, scrutiny of the annual returns in some of the past years shows that mention of the disease is 'conspicuously absent'.

The history of yellow fever in *Senegal*, as in the British West African Colonies, dates back to the early days of European settlement. A brief account, giving some of the main features, may be of interest. To go into them in any detail would savour of vain repetition. There seems to have been a singular periodicity in the outbreaks, Senegal being menaced in cycles, as it were, of ten, fifteen, or twenty years. Thus, in 1778 Gorée lost 60 out of 93 Europeans. Fourteen years later, in 1792, 200 British troops attempted to occupy the island of Bulam and 90 per cent of them (180) died in a few weeks. In 1816 the troops at Gorée were more than decimated. Fourteen years afterwards (1830) 144 Europeans were attacked out of a total of 152, and 52 died, and the same year at St. Louis 328 out of 650 Europeans died and among these 10 out of 12 doctors. From the few cases in

which we have the clinical history the course seems often to have been very acute. Thus, in 1850 we have the following laconic report. A Frenchman landed in Senegal and contracted the disease within a month. He sent in the following written message: "Suis atteint fièvre jaune, j'espère." Two days later "Mal évolue, état grave." Next day "Il ne vous reste plus qu'à prier pour moi, adieu." Death took place early on the fifth day of illness.

In 1859, again at Gorée, of 267 Europeans 244 were attacked and 162 died. In 1878 an outbreak involving the whole of Senegal occurred and 1474 Europeans suffered, of 26 medical men in the service 22 succumbed. A fresh epidemic decimated Dakar in 1900, after which there was a longer free interval without any outbreak of an epidemic nature. In 1926-7 further cases began to be reported—from Tivaonane, M'Bour, the aviation camp at Onakam, and at Thies, and in the latter half of 1927 52 deaths occurred among 77 attacked at Dakar. In March 1929 a report issued at the Dakar Conference gave the following history, in abstract.

Between the 13th May and 25th December, 1927, there were 190 cases and 135 deaths, a case fatality of 70.89 per cent. Europeans, as would be expected, suffered most—133 cases, 88 deaths—Syrians next, 44 cases, 32 deaths. The white population was stated to be 9595. In addition to these cases which were definite, there were 30 others, classed as 'suspected,' and of these 20 died. Twelve of these were 'concealed' cases, nearly all Syrians, kept hidden by their compatriots to escape sanitary measures, 11 of these died. The means of prevention adopted were based on tracking down carriers of the virus and isolating them under *grillage*. At the first alarm the '*régime du danger imminent*' was applied and all the territory of Senegal was thus treated by an order of the Governor-General on 15th October, under this order every dwelling occupied by susceptible inhabitants had to be provided with a *chambre grillagée* for sleeping quarters.

The Governor-General appointed a permanent Yellow Fever Commission with the Secretary-General of French West Africa as President. The clinical aspects of the disease were specially studied by Professor Pettit, experimental transmission of the infection to monkeys was performed by Dr. Sellards of Harvard University, who went to Dakar from Monrovia for the purpose, and the Inspector-General of the Health Service was in touch with members of the Rockefeller Foundation and with the Director of the Health Services of the Gold Coast and Nigeria.

We will not pursue the history of the investigations further at the present time, for it is more fittingly dealt with in a later section devoted to a description of recent developments. These developments took their rise in the work of the West African Yellow Fever Commission which was organized by the Rockefeller Foundation in 1925 and although it may be thought that their early findings should hardly now be regarded as belonging to, or be included in, recent developments, this work will be more fully considered there as an intermediate stepping-stone between the old ideas and the new.

To sum up we may say that yellow fever has been of far more frequent occurrence than is usually believed on the West Coast of Africa. There were, it is true, a few gaps in the past century in which no case was seen, but, nevertheless, there was not long enough interval to warrant the supposition that the infection ever died out. Though it might have been maintained by frequent reintroduction, it was probably endemic. From official reports the disease is seen to have been present during the century in the following years: 1813, 1815, 1831-4, 1843, 1848-9, 1851, 1853-5, 1857, 1860-1, 1869-71, 1874-7, 1879-82, 1885-9 and 1892.

So far a few of the main points in the history of yellow fever have been given from the epidemiological aspect, directing attention to some of the more noted outbreaks which have occurred in certain parts of the world. In the sequel many other facts of historical import will emerge when an account is given of the older ideas as regards ætiology and the discoveries as to the mode of conveyance and contraction of infection, and later recent research work on the virus.

In more recent times there have been noteworthy variations in prevalence as compared with earlier years. In Africa infection was present from Senegal in the north to the Belgian Congo in the south, in 1927. In Senegal 117 cases were recorded and 111 deaths, a tremendous fatality rate, and in the Gold Coast 40 deaths among 107 persons attacked. After that date there was a gradual diminution and in 1931 there were only four suspected cases and one death, all in Mamfe Province, Cameroons.

In South America, on the other hand, there has been a marked increase, with epidemics in Rio in 1928 and 1929, and cases also in other parts of Brazil and in Colombia. In 1931 reports were received of cases occurring in thirteen widely scattered localities.

situated between the State of Rio in the south, Ceará in the north, and Palma inland. Investigations could not trace connections between these, a fact which suggests that infection may persist for a long time in the interior of the country without revealing itself by epidemic outbreaks. Seeing that foreigners were mostly attacked it is a valid inference that infection was persisting in a more or less latent state among the native population. Clearly under such conditions commercial air-services become a potential danger, unless routes are laid down avoiding, if possible, infected zones, or special precautions are taken and anti-amaryl aerodromes erected.

The Brazil outbreak in 1928-9 was very typical epidemiologically. A soldier was taken ill and died, his disease being diagnosed as influenza. Three days later another soldier died, and two more in the last week of May. In June there were 52 cases, in July 40, and a few during the later months of the year, but a total by the end of December of 125 cases, 73 fatal. In January 29 more were reported, in February 54, in March 241, April 190, May 87, and then a rapid drop, in June 9, in July 1, in August none.

F. L. Soper has shown that although visible urban and maritime outbreaks may decline and even cease entirely for a time, there is a vast silent reservoir of infection in the interior of South America.

Yellow fever infection carried by *Aedes ægypti* has been much more widespread in the interior of north-east Brazil than was believed, even though this area had long been under special observation. Aedes-transmitted fever in this area did not disappear following organization of anti-Aedes campaigns in the principal centres of population.

Yellow fever endemicity, instead of being limited to the coast of north-east Brazil, as had been the general opinion, extends to all of Brazil except a few of the Southern States, to Bolivia, Paraguay, Peru, Ecuador, Colombia and Venezuela, and involves many districts in which *Aedes ægypti* is not found (see later). There is no evidence of recent outbreaks in any of the important Pacific or Caribbean ports of South America.

A chronological list recording the dates and characters of yellow fever outbreaks would be both interesting and useful. Interesting in that it might help to solve the long-debated question, a question even now not settled to everyone's satisfaction, as to the place of origin of yellow fever, useful in that others would be saved what has been at times a tedious research. There are, however, difficulties of no mean order in the way. First, early

records are meagre and all we have to rely upon are terms, often ill defined, used by combatant officers, or at all events non-medical writers, in describing their campaigns, second, yellow fever does not always present a clear-cut picture and the diagnosis might be at fault. Even to-day, with all the aids of modern scientific developments, accurate morbid anatomists, cautious immunologists, the diagnosis is not always easy, and in the earlier days of the sixteenth century descriptions were often vague and we have little to go upon. Thirdly, no one can have access to all records and when one has availed himself of opportunities offered to study all within his reach and drawn up his list, another with access to other records will find much to add and lacunæ to fill.

After a brief consideration of certain difficulties in diagnosis presented by early descriptions of outbreaks of disease which exhibited some of the features of yellow fever and may or may not have been that disease, we will give a list, so far as our efforts have been able to compile one, of such epidemics reference to which we have been able to find, knowing, as has been said already, that such a list must be far from complete.

Apart from any discussion of symptoms common to yellow fever and other morbid conditions, the very multitude of its synonyms is an indication of the uncertainty of diagnosis. Some of these, in early days, were used as a cloak to cover ignorance, to satisfy people by giving a label to a condition whose essence was not known, others, in later, even recent, times as a cloak to cover knowledge, to keep secret the presence of a disease which, if known, would injure trade. Many of the synonyms are mere place names, such, for example, as Fernando Po fever, Bight of Benin fever, Sierra Leone fever, Magdalena fever (River Magdalena Colombia), Port of Havana fever (a name used in 1620), endemial remittent fever of Freetown, fever of Olinda (Pernambuco, 1685), or place names bestowed from the supposed source, such as Bulam fever (which attacked Grenada in 1793), *Maladie de Siam* (attacking Martinique in 1649), Kendal's disease (in Barbados, 1691), others again from some notable feature or supposed cause, such as Yellow Jack, Ships' fever (in sailing vessels with water in casks replenished at ports when larvæ and eggs of *Aedes* might be brought on board and a member of the crew become infected on shore), another synonym, *La fièvre matelotte*, testifies to the frequency with which sailors were attacked, Chabert in 1821 proposed the name *Maladie spasmodico-lipyrrienne*, Leipyria being a term applied first by Hippocrates and later by Galen to

a febrile condition in which the body seems to be burning and hot within while the limbs are cold Seasoning or Acclimatizing fever, Hepatic fever (Elmina, 1895), Black Vomit, vomito prieto, vomito negro, *Coup de barre* (Guadeloupe), Railway fever (in Guatemala when the way was opened to the interior towns of Zacapa and Gualun in 1905), or to hide the true fact or prevent panic among the people, such as *Febris malaria continua perniciosa nephrotica*, acute delirious malignant malaria, bilious remittent fever, endemial inflammatory fever of the West Indies, typhomalaria (in a report from Freetown to the Secretary of State, 1884) Of course, as we shall see shortly, some forms of malaria were confused with yellow fever Lastly, one ought not to be omitted, used formerly in Colombia, namely *Fiebre patriótica*, bestowed upon yellow fever because it removed foreigners

Schotte's account of the outbreak at St Lous, Senegal, in 1778, is one of the earliest detailed descriptions of yellow fever He mentions the severe initial headache, the general pains, the congestion of the eyes, the presence of petechiæ, the vomiting of black material and the coma preceding death—typical, in short, except that he mentions some of those recovering as suffering later from relapse of fever, these later attacks were probably malarial in nature He does not mention jaundice as a symptom but does so later when he discusses the diagnosis He calls it *synochus atrabiliosa* and states that it differs from 'bilious fevers' in severity of symptoms, in the occurrence of hæmorrhages, the presence of the petechial rash and the black vomit Schotte does not seem to look upon it as a disease of recent introduction, but rather as an infection of new arrivals attacked by disease already present The records of yellow fever in Yucatán and the French Antilles in the previous century on the contrary point to it as newly introduced and tell how the indigenous population also suffered and died

The disease occurring in Grenada in 1793 consequent on the arrival of the *Hankey* from Bulam was not regarded as the "malaria or yellow fever" [perhaps the writer means bilious remittent fever] of the West Indies, but as a new importation, and it was therefore called by the non-committal name of 'Bulam Fever' From this time onwards reports of yellow fever occurring in West Africa, from Senegal to Angola, are frequent, these parts were in fact endemic foci and the constantly recurring outbreaks were among the new arrivals at European settlements or the crews of ships touching at coast ports, especially those of Sierra Leone,

and thence cruising to the Gambia, Senegal, Cape Verde Islands, Ascension, St Helena and Europe

Points of distinction from malaria were becoming impressed upon observers in different parts of the globe. Thus Blair in 1816 calls attention to the prevalence of remittent fever cases side by side with those of yellow fever in Barbados, evidently imported cases of the former seeing that malaria is not a disease indigenous in Barbados. He states that among a garrison of 2310 there were 470 cases of remittent fever, 705 of yellow fever and only 36 of intermittent fever. Some of the first may have been enteric infections.

Uncertainty as to its distinction from malaria persisted long after observers had begun to suspect that they were two diseases and not merely different forms or aspects of one. One writer, as late as 1857, states, when attempting to define it. Yellow fever is a disease not proved as yet to be a disease *sur generis*—endemic only in low districts on the sea-coast but, under certain circumstances, sporadic in other places, rarely, if ever, appearing beyond 48° North or 27° South of latitude and but seldom above 2500 feet elevation, not without a temperature of at least 72° promoting its production and propagation, depending in part on causes unknown, but, in circumstances favourable to its extension, capable of being propagated by infection and prevailing in three different regions of the globe—America, the West Coast of Africa and Spain (south coast).

Attempts were made to differentiate yellow fever from bilious remittent fever by drawing up a list of the chief distinctive points

- 1 Yellow fever has a more insidious onset but runs a more rapid course than remittent fever

- 2 The shock to vitality is manifested earlier in yellow fever

- 3 Jactitation, mental depression, apathy and delirium occur earlier, as also does jaundice [but jaundice is not an early symptom of yellow fever, it is in bilious remittent, the author showed some confusion here]

- 4 Nausea and vomiting occur earlier and are more distressing than in bilious remittent, though retching is less

- 5 The pulse is distinctive, at first rapid, then soft and asthenic, then weak, unequal and irregular, and lastly slow

- 6 There is orbital pain, suffusion of conjunctiva, eyes bright, a drunken appearance with anxious expression

- 7 Sense of constriction in the chest with burning pain in the stomach

- 8 Livid and leaden-coloured patches on the skin

- 9 Suppression of urine

- 10 Lastly, the tint of the skin is distinctive and "would seem to depend on a stagnation of dissolved blood in the capillaries and not upon the colouring matter of bile as in yellow remittent [*i.e.* bilious remittent] fever"

This last was a shrewd observation, for a consideration of the points enumerated shows that the author was not altogether clear in his own mind of the distinctive clinical features. We must remember also that each symptom, taken singly, may occur in other conditions, and that it is easy to mistake black vomit for the dark green bilious vomit of malaria. It was not till 1738 that Henry Warren recognized 'black vomit' to be blood altered by the gastric juice. In Warren's words

The fatal black Stools and Vomitings are vulgarly supposed to be only large Quantities of black Bile or Choler, which false Notion seems to be owing to that fixed unhappy Prejudice that the Fever is purely *Bilious*. But let anyone dip in a Bit of white Linen Cloth, he will be soon undeceived, and convinced that scarce anything but mortified Blood is then voided, for the Cloth will appear tinged with a deep bloody Red or Purple of which I have made many experiments

Handcroft in his Goulstonian Lectures, 1811, argues *in extenso* that the black vomit is hæmorrhage from the stomach. There would be no need for him to dwell upon the point as he does if it were generally or even widely known. That it was not is clear from the fact that fifteen years later Dr James Johnson in his work, now regarded as a classic, on the *Influence of Tropical Climates on European Constitutions*, is only "inclined to accept" this view.

In his day the term 'bilious remittent' covered both malaria and yellow fever, but what was designated 'climatorial bilious remittent' was differentiated as developing among the crews of ships, in those who had perhaps not set foot on land. This was regarded as a noteworthy characteristic and Burton, who was surgeon to the Royal African Corps, writing in 1842, lays stress on this as being generally accepted, that one attack conferred immunity against a second which was not the case with malaria.

Bilious remittent and yellow fever occurred together. When in epidemic form or accompanied by black vomit it was called yellow fever, otherwise simply climatorial or endemic remittent fever," but there were all degrees of severity from *embarras gastrique* to yellow fever.

Trousseau in his *Clinical Medicine*, about the middle of last century emphatically protested against the doctrine, which at the time had gained a considerable prominence, that there was a similarity between malignant jaundice—which he regarded as analogous with typhoid and the bilious fever of tropical climates—and yellow fever. Early in his career Trousseau saw a good deal of yellow fever and in differentiating he states, and here we

sec an example of his clinical acumen, the main point is the absence of jaundice in yellow fever "In upwards of a thousand yellow fever patients who came under my observation," he writes, "not one had jaundice," and later

When we proceed to compare malignant jaundice with yellow fever, looking to the symptoms and anatomical lesions irrespective of the jaundice, it seems surprising that cautious and experienced physicians should regard as similar two affections which present such different characteristics, but the astonishment ceases when it is borne in mind that those who have instituted this comparison never saw the epidemic, and that those who had studied yellow fever only know by books the malignant jaundice with which they compared yellow fever

In 'real jaundice' the urine always contains a large quantity of biliverdin and acquires a still deeper colour on addition of tinctura iodi and nitric acid, this is not so in yellow fever, the urine may be red, is often suppressed, but "never contains the colouring matter of the bile" We know now that this is not quite correct, the reaction may be obtained on or about the fifth day of disease and, if present, is usually regarded as a favourable prognostic

We shall go more fully later into the confusion that used to exist between yellow fever and some forms of malaria, here we may say a few words on other diseases which obscured the diagnosis *Relapsing fever*, a common disease of the tropics, may in some epidemics strongly resemble yellow fever There may be deep discoloration of the skin, hæmorrhages occur and, if gastric, may be altered by the juices to a dark, coffee-ground character, like 'black vomit' Important diagnostic points would be the fact that the negroes would be equally liable and the fatality rate would be as high as in Europeans, and relapses, if present, would differentiate McAuliffe states

I even believe that it would be impossible to clearly distinguish these affections if both raged at the same time in a community [as they did in 1923 at Bucamaranga, Colombia] Certainly outbreaks where black vomit is common may be due to spirochætosis, but if the fatality or even the morbidity is much lower among negroes the infection is almost certainly yellow fever

Hæmorrhage from the gums and into the skin is a symptom common to yellow fever and to *scurvy*, also scurvy, as we have seen, occurred in outbreaks on board ship, not early, however, as is usual with yellow fever, but late, after 4-6 weeks' voyage Moreover, recovery from yellow fever is rapid and complete, in scurvy, unless proper food and treatment are available, amelioration is but temporary

Typhus again, though the exanthematic fever is conveyed by lice and is commoner in cold weather, has been considered to be "yellow fever modified by climate and marine conditions" The endemic form, *el tabardillo*, of the Mexican highlands has a high mortality and prominent symptoms are hæmatemesis, epistaxis and jaundice

It will be convenient to discuss here the disease described by Chisholm as "Malignant pestilential fever, commonly, but improperly, called Yellow Fever" He designates it the most tremendous of all the tropical diseases and believed it to be "the typhus of Europe grafted on the yellow remittent fever of the torrid zone," and "the symptoms are surprisingly combined" His account is full of interesting detail and is historically worthy of record In his view, typhus of cold climates, plague of warm and the malignant pestilential fever of the tropics derive their origin from a specific virus, modified by climate, but interconnected by a regular gradation in intensity He adduces the following in support of his affirmation Persons left England to colonize the island of Bulama on the African coast, they died of typhus Their clothes and bedding were introduced into Grenada by the ship *Hankey* in 1793 and there broke out the "symptoms of yellow remittent fever superinduced on those of typhus" This fever later devastated the West India Islands, the personnel of the British Army and Navy stationed there, and spread to the chief cities and towns of the northern United States and later to Spain Doubtless repeated introduction of infection took place, for ships were often very crowded, the people were poor, had no change of clothes and were dirty in their habits—it was difficult to be otherwise on board in those days The name given to the disease by the natives of San Domingo and parts of South America was *chapetona*, a word signifying brigand or 'robber' and applied to the Spanish invaders and to the disease which they were thought to have introduced M Jonnés has studied the question and affirms that he has been able to trace 140 irruptions of it in the eighteenth and 102 in the nineteenth centuries The disease has been confined between 8° and 46° north latitude and 8° and 29° west longitude "About one in three and a half perished by this dreadful scourge from the first appearance of it at St Domingo to the last year (1820)!"

Then follows an account of the symptoms In severe cases violent vertigo, the patient falls down almost insensitive, body cold, covered with cold sweat, then intense heat with quick, small, hard pulse, intense headache, præcordial oppression, eyes

inflamed, watery, rolling, face flushed, heat at epigastrium soon followed by nausea, retching and vomiting. Then intolerable pain in back and calves. Symptoms increase for 12–36 hours, then cold sweat, coma, delirium, followed by a remission when the patient says he feels better, but soon a convulsion comes on and he dies, or he may temporarily revive and die in a second fit.

The delirium is a sort of 'drunken state' like that of plague. At the post mortem in a man comatose on the third day and dying on the fifth "the cranium, on being sawed and prised up by a chisel, was so pressed from within by the distension of the cerebrum as to fly off as if a spring from within had acted upon it." The serous fluid was in excess.

Also on the skin there appeared patches of red or livid spots at the start of the coma or a few hours before death, these usually were seen on the neck, chest and shoulders, but occasionally as larger "blotches rather than petechiæ." If this occurred the case always ended fatally. The pulse was slow, down even to thirty per minute. The tongue might become dark to black shortly before death. Hæmorrhages might be profuse, surpassed only by those in scurvy—from nose, mouth, anus and urethra, and even the canthi of the eyes. Stools may seem to be pure blood, sometimes there was gangrene of the scrotum. Vomit towards the end was black "like coffee badly boiled." Buboes were not frequent, occasionally in groin or axilla, but more often the parotid. Death might take place in thirty hours from the start of the fever, but more usually on the fifth day, sometimes not till the ninth. Those who recovered began to improve between the seventh and ninth days.

Some patients suffering from dysentery were admitted to the hospital in Grenada, into a ward where there were cases of this "pestilential fever." The dysentery cleared up, but the patients were attacked with the fever. If pregnant women were attacked they usually died. Post mortem the liver was found shrunken, buff-coloured, the skin was not yellow, but "dingy as after bruising."

In commenting on this Chisholm regards it as "certainly contagious." "I could demonstrate the affinity between the malignant pestilential fever and typhus on the one hand and plague on the other, by a colation [*sic*] of their distinguishing symptoms." He notes "the extremely rare occurrence of re-infection," as well-established in the West Indies, North America and Spain. "In 4400 pestilential cases Dr P

Russell found only 28 of re-infection " He adds the shrewd comment

I am well aware that it is a general observation that the yellow remitting fever of the West Indies attacks only once, but this observation extends only to those persons who uninterruptedly reside in the climate, for an interval of a few months spent in a cold climate or even, in some instances, in another island, the local circumstances of which are different, renews the disposition to be acted upon by the causes, and, consequently, creates an aptness, unless the utmost prudence is observed, to the recurrence of yellow fever This exhibits a strongly marked distinction between the yellow remittent and the fever before us [That is, the malignant pestilential fever, which, it will be noted, bears many resemblances to typhus fever]

"Great heats alternating with frequent showers of rain" are most favourable to producing yellow fever, he asserts

It is not clear to us what was the actual disease covered by the term 'malignant pestilential fever' Chisholm treats in fair detail the characteristics but they do not fit in very well with any disease known to us at the present day He notes that sailors are particularly predisposed to the infection, probably because of a 'scorbutic taint,' and negroes least liable Again, those newly arriving from Great Britain, and the plethoric, the robust and the intemperate suffered most Thirdly, the incubation period is said to be up to four days These three points are in favour of yellow fever A discussion of other characteristics mentioned would, however, seem to exclude this disease Close contact, for example, is stressed, or, as Chisholm states it, contagion is from the bedside of the sick, the best way of escaping infection is staying away from an infected house, though mere entering the sickroom without approaching the patient has never communicated the infection [this indicates typhus and lice vectors], but an approach so close as to "notice the foetor of the breath, or to touch the bed clothes, occasions nausea, headache, and after an interval of hours or days, the disease itself" Actual contact is almost certain to produce the disease and "touching the wearing apparel of a patient or a covering of a patient communicates infection" [this has been disproved as regards yellow fever, as we shall see later] Effluvia are infectious, if the visitor approaches near the patient, but not beyond 6 to 10 feet at most Finally, and this would seem to exclude yellow fever altogether, "the contagium may and actually does attach itself to everything surrounding the sick, their bed-clothes and wearing apparel more especially, and thus may be conveyed from one country to another"

He gives an account of an outbreak on board a ship and others

of individual cases, but although related in considerable detail they present no readily soluble problem. These may be referred to briefly. The ship outbreak occurred on the transport *Flora* at Barbados. From the start of the voyage infection with malignant pestilential fever seems, he says, to have been on board, for a fortnight before embarking her crew and troops she had landed French prisoners from the West Indies, and it was thought that they brought the infection. Fifteen men were attacked in a single night and in the ensuing two days forty-eight more. The sick were landed at Spike Island hospital and the contacts at Haulbowling Island where they were encamped for three days. The vessel was fumigated and cleaned, all berths taken down and new hammocks and blankets served out to the troops. With a total complement of 183—144 troops, 6 officers, 22 ship's company, 11 women and children—all in good health, the voyage was resumed. Four days after embarking and within 24–48 hours after sailing 7 were taken ill, and one died on the eleventh day of illness and by that time 23 had been attacked. In all more than 70 were infected and 3 died. Chisholm says in another place that this fever killed 1099 out of 5000 infantry comprising the army for San Domingo. This scourge has always been regarded as yellow fever.

The treatment adopted is worth quoting as indicative of what unfortunate patients had to submit to in the early years of last century. The aims were three: (1) to empty the alimentary canal of acid offensive matters to prepare it for reception and absorption of mercury, (2) to obviate the inflammatory diathesis, and (3) to restore natural tone and energy. The second of these is the most important and the only one with which we need concern ourselves. Of course, bleeding is recommended, but unless the patient is young and robust this should not be done in the early stages. One would think that later the degree of debility would be an even stronger contra-indication. In 1812 at Brimstone Hill early bleeding was adopted and of 422 so treated 118 died. Most important, in fact the sheet-anchor in this disease was, in his opinion, *mercury*. "I did not lose a single patient in whose case it was pushed to the full extent," writes Chisholm. He started with 10 grains of calomel and 10 grains of jalap, as an aperient, and repeated the calomel every three hours. Salvation usually came on in twenty-four hours. Bark is bad, he found, "nature revolts at the very idea of bark." Salvation was regarded as necessary and no cure was complete in which this had not been produced. A French doctor, named Amie, reports a case of malignant pestilential fever, called by him 'yellow fever,' in which

he gave 64 grains of calomel by mouth, 2040 grains as 'lavement,' 3600 byunction, a total of 5704 grains, in five days, and he comments "the patient recovered rapidly" In another regiment whose doctor did not know of this intensive mercurial treatment many died of the disease, whereas another lost only two out of forty-five patients so treated

He regards mercury as "the Samson of the *materia medica*" In some cases a comparatively small quantity would excite salivation, in others, and particularly in 'malignant pestilential fever,' 6000 grains might be necessary He quotes the case of a sergeant-major of the Royal Artillery suffering at Martinique from "yellow remittent fever," whose illness began on 1st July, 1798 He was bled freely and calomel administered at the onset On the 4th he took 60 grains of calomel, 10 grains every two hours, "without sensible effect," and blisters were applied to the inside of his thighs and the surfaces dressed with mercury ointment, on the 5th he was bathed in a cold, clammy sweat and was vomiting black matter "like coffee grounds" The next day his pulse was 110 per minute and feeble, and vomiting was continuous Injections [presumably rectal] containing half an ounce of calomel were given every four hours, day and night On the 7th the vomiting ceased, the pulse gained strength, improvement was sustained and recovery ensued

One more case of yellow remittent (malignant pestilential) fever may be quoted, as the treatment was a little different, but equally drastic It is one of several detailed by Chisholm The patient was a Scotsman of 22 years who had been in Demerara five months On 1st August he had fever, temperature 104° F, pulse 100 per minute He was given bark on three occasions but as he vomited each time it was stopped So

At 1 p m poured over him about 6 gallons of water in which a pint of salt was dissolving and wrapped him in a blanket (T 102° F, pulse 100) At 6 p m two pailsful of water with salt thrown over him—much relieved On August 2nd about a dozen stools with much griping, temperature 6 a m 100°, pulse 101 Five large pailsful of sea water dashed over him Temp 99°, pulse 98, perspired and slept At noon, T 102°, pulse 100, sea water treatment repeated, T 98°, pulse 100 At 6 p m T 102°, pulse 101, water treatment repeated, T 96°, then 98°, pulse 98 3rd August 6 a m T 100°, pulse 99, same dashing of water and he was also immersed for a few seconds T 92° but in ten minutes 98°, pulse 92 Hot bottles needed to restore natural heat to the feet 1 p m T 102°, pulse 116–120, bathed as before Calomel 20 grains at bedtime, also blister and friction with mercury After a week of this treatment the patient began to improve and recovery was rapid

The author sums up as follows "He took into the stomach 64 grains calomel, 2040 grains by clyster, with bark two table-spoonsful, by friction 16 ozs of strongest mercurial ointment or 4448 grains according to the London Pharmacopœia of the day," in all 6552 grains "It may be difficult in this case to determine whether the cure was effected by cold bathing or mercury or bark, or by a combination of the three"

Chisholm comments in these terms

An argument not unfrequently brought against the use of mercury in the malignant pestilential and yellow remittent fevers is founded on the uncertainty of its operative effect Thus, it is said that a few grains will excite salivation under certain circumstances, whilst a thousand are not sufficient to produce the effect in cases of the fevers before us, and that therefore a medicine of so variable an action should not be relied on in circumstances so dangerous I admit the fact, because I have seen it happen, but I deny the inference under the use of every other mode of treatment the mortality in malignant pestilential fever has been dreadful, one in three and a half

To determine what this condition was is certainly a puzzle, all the available evidence points to its infectivity Thus, we have the record of a captain who, in working his ship out of harbour, sent five of his men on board another, on which 'malignant pestilential fever' was present, to fasten a warping line All five were subsequently attacked and three died By prohibiting intercourse of the two survivors with the rest of the crew, that is by segregating them, attending them himself and taking the precaution of changing his clothes when visiting them, and later having their quarters washed and frequently fumigated with moistened gunpowder, boiling tar, etc, by destroying the bedding and wearing apparel of the five attacked, the captain was able to report that there was no further extension of infection In other ships where such precautions were not observed, relapses or extension of the disease were common Thus, as a case in point, a vessel from Liverpool captured a French ship in May 1793 On arrival at Grenada the men were distributed among merchantmen in need of crews, i.e. the least cleanly and most highly infected ships All the drafted men caught the infection and died Also, it is said, the crew of the English vessel, who were till then in good health, were allowed to visit the shore at will and the infection was thus brought back to the ship No measures were taken to extirpate the infection or even to check its progress, it spread unrestrainedly and in two months nearly the whole crew perished

The crew were chiefly young men, and in the full enjoyment of health and vigour—but the master was unfortunately one of those men who, with intrepid bravery, possess a sovereign contempt of all those measures which prudence dictates for the preservation of health and prevention of infection

In spite of the description by Schotte in his treatise on *Synochus atrabiliosa*, already referred to, recognizing a distinction between yellow fever and malaria, the error took long to dispel. Belief in their identity received powerful support from the endorsement of the Second Report on Quarantine, of the General Board of Health 1852, regarding yellow fever. The Board decided that yellow fever was not communicable from man to man or from ship to shore and, in spite of the strong opposition of Sir William Pym, Inspector-General of Naval Hospitals and Superintendent-General of Quarantine, who probably knew more about yellow fever than any other European of his day, refused to consider any evidence to the contrary

We must, in justice, not omit to say that four years before Pym had used the terms Bulam Fever and 'vómito negro fever,' reserving 'yellow fever' for severe malaria of the bilious remittent type, as Chisholm had done nearly half a century earlier. Ferguson, however, in 1839 (*Observations on Yellow Fever, London Med Gaz*, 1839, p. 838) used the term yellow fever for severe fatal outbreaks and malaria for the less fatal. Incidentally, the malaria outbreak which wrought such havoc at Walcheren was called yellow fever

The diagnosis was not by any means always easy in the days before the microscope was brought into use for diagnosis and we must not forget that in the Western hemisphere most places where yellow fever occurred were also malarious, and also in Senegal and the Gulf of Guinea malaria was very prevalent and very severe when Europeans first visited and traded there, and further, at that time Europeans were not sufficiently numerous at any place on the West Coast to make an outbreak of yellow fever easily distinguishable from one of malaria

The epidemic of Freetown, Sierra Leone, in 1884 is a good instance of the reluctance to diagnose yellow fever in early years, we see in the report how the fear, the reluctance gave place first to stronger suspicion and finally to frank acknowledgment as confirmatory evidence was forced upon the observers. During May and early June a form of fever described by the Acting Colonial Surgeon as *typho-malarial fever* became prevalent, Europeans, it was noted, were particularly subject to attack. As in many out-

breaks the early cases are often of a milder type than those coming after. Malignant symptoms, it was stated, became more marked from day to day, and towards the end of June, on the 27th, the Acting Colonial Surgeon reported the disease as "*a pernicious remittent fever on the borderland of yellow fever*," and a private practitioner of Freetown gave it as his opinion that "the fever in question had already assumed the form of *yellow fever of a mild type*." Next, the senior military medical officer reported a death from yellow fever, the victim being a soldier in the West India Regiment. On 28th June the Acting Colonial Surgeon reported a European as dying of *black vomit*, and four days later the same medical officer reported the deaths of two Europeans, giving as the cause *Yellow Fever*.

A more recent instance of confusion between yellow fever and malaria is the outbreak in Australia in 1864, but in this case it was not yellow fever masked under the name of malaria but malaria reported as, or thought to be, yellow fever. 'Black sickness' was introduced that year into Burketown by Malays and fifty died in a small settlement with a population of seventy-six. The disease, which was virulent malaria of the bilious remittent type, was believed at the time to be yellow fever and is still, we understand, spoken of as 'yellow Jack' by the older residents.

To bring the question of clinical diagnosis down to recent years and to obviate having to return again to this, mention may here be made of a peculiar condition reported from the Kukuruku division of Nigeria at the end of 1928. It broke out in epidemic form, the chief symptoms being chills, fever, headache, general pains, nausea, vomiting and jaundice, the last appearing between the second and the fifth days. Albuminuria with casts occurred, but not as a rule to the degree seen in yellow fever. Pathologically, the liver showed changes very like those regarded as characteristic of yellow fever, and the material present in the stomach was like the 'coffee grounds' of *Vómito negro*. Laboratory animals could, however, not be infected, nor did the serum of recovered patients give the mouse protection test (see later). The fatality rate was only about 5 per cent. In short, no diagnosis was reached, those investigating it believed that they had been able to exclude yellow fever, Weil's disease, relapsing fever, acute yellow atrophy of the liver and catarrhal jaundice.

Before the researches of the present century established serological tests for determining the diagnosis of yellow fever, reliance had to be placed on clinical and epidemiological evidence and the following is a summary of that evidence as the stand-by or criterion

in what may be called the intermediate period between the time when most febrile conditions in the tropics were ascribed to malaria and that of advanced serological and experimental study of the last quarter century. The summary serves to show that epidemiologists and clinicians were differentiating them on general grounds :

I *Epidemiological Differences*

Yellow fever is a disease more of towns and cities, malaria of rural or suburban districts. Yellow fever is common on the coast and on board ships and is contracted in places where malaria is not known such as Barbados and Ascension Island. Blair was much struck by this as a distinguishing feature. He says

It is remarkable that some of the most destructive outbreaks of yellow fever have occurred amongst troops at stations where intermittent fever is almost unknown as indigenous. For instance, Brimstone Hill in St. Kitts, Port Charlotte in St. Vincent, St. Ann in Barbados, and *vice versa*, those colonies in which ague is most common have been least frequently visited by yellow fever—for example, Demerara and Berbice.

In this, of course, he was too sweeping, making too rash a generalization, in Jamaica, for instance, and in Cuba both diseases used to be very common.

Again, an outbreak is limited unless newcomers are introduced, patients do not suffer from relapses or recurrences as do malarious subjects, and old residents are often immune. The fatality rate of yellow fever is high among Europeans, higher than is seen in malaria [but when first introduced the fatality from malaria may be very high, in the Mauritius epidemic of 1867-8, out of a population of 80,000 in Port Louis 22,231 died in thirteen months and as many as 234 in a single day, and deaths in the island numbered 31,920 from this cause]. Fatality among the negro population is usually low in yellow fever, it is also less than in the white in malaria, but the difference is not so marked, finally, it was noted that the death-rate among children was less than among adults, the opposite of what occurred in malaria.

II *Clinical Differences*

Yellow fever usually began suddenly with severe pains at a time when the patient was in good health, fulminating cases with early death were rare and the course of disease was in most cases short, death occurring in 5-7 days or recovery then setting in, death often was associated with convulsions or coma. If death occurred within twenty-four hours, the cause was more likely to be malaria, though coma and convulsions are observed in malaria,

such do not constitute a majority In yellow fever vomiting may be persistent and becomes the characteristic black vomit, hæmorrhages occur from the mouth and elsewhere, jaundice is fairly late When recovery begins the weakness is very marked, but convalescence is rapid In malaria convalescence is slow and is often incomplete, there is residual anæmia and pallor, jaundice when it occurs is an early symptom and persists for a longer time

To epitomize In an established colony with a settled mode of living, if there is much sickness and a high fatality rate, affecting chiefly new arrivals and not presenting relapses or recurrences, this is evidence in favour of yellow fever as against malaria If mortality among the children of the residents keeps high, malaria is more likely to be the cause than is yellow fever, the latter does raise the death-rate among children but not with the 'steady persistence' of malaria

3 EPIDEMIOLOGY

Enough has been said concerning the uncertainty of diagnosis in the earlier days when yellow fever was beginning to be regarded as a disease distinct from marsh fevers, relapsing fevers, and so forth, and we will now proceed to give a list of outbreaks of which we have been able to trace records, acknowledging once again that this list is incomplete and that those who have access to larger libraries will find some omitted

Year	Place	Remarks
1493	San Domingo	Said to have exterminated the population of Ysabella
1585	West Africa	Drake reported losing 200-300 of his men when on the Coast, we have no proof, only surmise, that this was yellow fever The enterprise was known as Drake and Carleill's expedition to St Thago A thousand men were landed and they stayed ten days The men sickened soon after setting sail again and 200 or more died That the infection was probably yellow fever is favoured by the high fatality rate, the prevalence on ships after being anchored near the shore, and the practical certainty that infection had been acquired at the port
1599	West Africa	Sickness and mortality among the officers and men of Van der Does's expedition at Gran Canaria and São Thomé point strongly to yellow fever They were six days on shore at

Year	Place	Remarks
		Gran Canaria, three more days in harbour, then another six at Gomara. Fifteen died on the passage to São Thomé, and at São Thomé a thousand sailors and the Commander-in-Chief died. Altogether there were 15 deaths among the Captains of the land and sea forces and 1200 among the soldiers and sailors. On the voyage between the Canaries and São Thomé, the infection was limited to a few ships. Those attacked at São Thomé were almost certainly cases of yellow fever. Some ships returned to Holland and men fell sick on reaching the colder latitudes, these were most likely malaria infections.
1606	At sea on the way to Virginia	Bascome in his <i>History of Epidemic Pestilence</i> says "A mortal pestilence broke out in the fleet of Sir Thomas Gates and Sir George Somers, who were on their way to Virginia, in America. It was a spotted fever, with yellowness of the skin, attended by bilious vomiting, hæmorrhages, etc., symptoms which characterize yellow fever in the present day. It raged with an intensity equal to the true plague. It was preceded by bad weather and gales of wind lasting four days, which, with the crowded state of the ships, was sufficient to account for all their sufferings. The vessel in which Sir George Somers embarked was wrecked on the island of Bermuda, where Sir George died of the pestilence."
1620	Cuba	Yellow fever is said to have broken out in this year and to have continued with varying intensity for the next twenty-eight years. I have not been able to discover any details.
1624	West Africa	Much sickness and high mortality among members of Menezes's expedition, history closely follows that of Drake's expedition to St. Thiago in 1585 (v s).
1629	America	'Yellow pestilence in America' noted by Walford, but without details.
1635	West Indies	At Guadeloupe where it was known as ' <i>coup de barre</i> ' (see p 288).
1638	West Africa	Expedition under Mascharenas, history repeats that of Drake's expedition in 1585 and of Menezes's in 1624.
1640	South America	Among the Spanish population.
"	West Indies	Guadeloupe, French West Indies, recorded by Dutertre.
1646	West Indies	Rife throughout the West Indies, especially Barbados and St. Kitts, 1200 are said to have

Year	Place	Remarks
		died of it in these two islands Obviously, among such a number there must have been many blacks, who were therefore at that time not immune—an indication of recent introduction of infection
1647	Barbados	Noted in Ligon's <i>True and Exact History of the Island of Barbadoes</i> , published in 1657 This was very likely the same epidemic as that just noted, for it was thought by him to be the first appearance of the disease in the island
1648	West Indies	St Kitts Probably not a fresh outbreak, but a continuation of that of 1646, mentioned above Guadeloupe, French West Indies
„	Yucatán	This is looked upon by some as the first New World outbreak to be identified with certainty as yellow fever (see above, p 285)
1649	West Indies	Martinique, described by Père Labat
„	West Indies	Barbados, in this outbreak, as in that of 1646, it was noted that the coloured population was attacked equally with the white
„	West Indies	Cuba, Havana especially, and prevailed there for the ensuing five years
„	Spain	At Gibraltar, brought by ships <i>en route</i> to the West Indies from Africa, or returning
1652	West Indies	St Kitts, mentioned by Mauville de St Michael in his <i>Voyage des Iles en Amerique</i>
1655	West Indies	Jamaica, possibly directly introduced by slaves from West Africa, or by commerce with Cuba near by
1656	West Indies	San Domingo, reported by Moseley and by Moreau
1664	West Indies	St Lucia, severe and all but eighty-nine died out of an army of 1500
1666	West Indies	San Domingo (Haiti) and other West Indian islands
1668	America	Particularly destructive in the cities of New York and Philadelphia About this time intercommunication between settlements in North America—British, French and Spanish—and corresponding settlements in the West Indies was frequent and the old wooden ships would harbour mosquitoes
1671	West Indies	In Jamaica, recorded by Trapham
1686	West Indies	Attended by high mortality especially at Martinique Thought to have been introduced by the warship <i>Oriflamme</i> which had come from Bangkok, hence the name <i>Maladie de Siam</i> (see above, p 289) Spread from Martinique to

Year	Place	Remarks
		other West Indian islands Outbreak which may very likely have been yellow fever occurred in towns of the Brazilian coast and continued with varying activity for seven years
1690	America	Especially virulent in Charleston, South Carolina
"	West Indies	At Barbados and San Domingo
1691	America	Severe in Boston
"	West Indies	In Barbados where it was known locally as <i>Kendal's disease</i> or the New Distemper It was believed to have been introduced from Pernambuco
"	West Indies	In Jamaica and other islands An earthquake in Jamaica is reported to have caused the deaths of 2000 in Port Royal, mosquitoes and flies appeared in swarms and yellow fever killed another 3000
1693	America	In Philadelphia, Charleston, and, perhaps, Boston It is so recorded by Webster and by La Roche, but others think that a more southern port, Newport or New York is more likely
1694	West Indies	Barbados and elsewhere, perhaps in Barbados this was a continuation of the 1691 outbreak In Martinique the seamen and troops of Sir Francis Wheeler's expedition suffered very heavily
"	America	Many deaths in Boston, New York, and Philadelphia Later it was especially fatal in Connecticut and New Hampshire
1695	West Indies	Bermuda, San Domingo and Martinique
1699	America	Attacked Anglo-Americans in Charleston and Philadelphia "The disease which affected the Anglo-Americans was considered to be similar to, and as severe as, the epidemic which had devastated Barbados a few years previously," writes Bascome
"	Mexico	Vera Cruz attacked, thought to be the first epidemic here
1700	Spain	According to Hirsch the first record of yellow fever in Cadiz
1701	Canary Islands	No details, but slaves were brought by the Portuguese and Spanish vessels to the Canaries from St Thiago and the Guinea Coast, for the Canary Islands were ports of call between Africa and the Peninsula Outbreaks may have occurred earlier, but there are records of one in this year and of others in this and the succeeding centuries
1702	America	Outbreak in New York in August and September

Year	Place	Remarks
1703	West Indies	Outbreaks in Guadeloupe and Martinique, French West Indies, recorded by Père Labat
"	America	Outbreak in Charleston is mentioned by Howatt in his <i>Account of the Rise and Progress of the Colonies of South Carolina, 1779</i>
1705	West Indies	In San Domingo and Martinique, continuing in the latter until 1706
1709	America	In this and the following two years several places on the coast of South America were attacked. In the Brazilian territory it is said that vast numbers of all complexions were carried off. There was, therefore, no established immunity among the coloured population
1715	America	In North America, causing a mortality, so a report stated, equal to that of the plague in London in 1665
"	West Indies	In Barbados, Griffith Hughes's account of this outbreak (<i>Natural History of Barbados in Ten Books</i> , published in London, 1750) is very graphic. It disproves Warren's belief that yellow fever is "a species of plague, brought to Martinique in bales of goods from Marseilles in 1721." The "new distemper," pestilential fever, bilious fever, Kondal's fever of 1691 was certainly yellow fever (vs). The following is Hughes's description: "The patient is commonly seized with a shivering Fit, as in an Ague, which lasts an Hour or two, more or less, and the Danger is guessed at, according to the Severity and Continuance of the Ague. "After the shivering Fit, a violent Fever comes on, with excessive Pains in the Head, Back, and Limbs, Loss of Strength and Spirits, with great Dejection of Mind, insatiable Thirst and Restlessness and sometimes too with a Vomiting, attended with pains in the Head, the Eyes being red and that Redness in a few Days turning to a Yellowness. If the Patient turns yellow soon he hath scarce a chance for Life, and the sooner he does so the worse. The Pain in the Head is often very great, when first seized with this Fever. After some days are past, this Pain abates, as well as the Fever, and the Patient falls into a breathing Sweat [he does not explain what he means by this] and a temperate Heat, so that he appears to be better, but on a narrow view [that is, on close inspection], a Yellowness appears in his Eyes and Skin and he is visibly worse. "About this Time he sometimes spits Blood, and that by Mouthfuls, as this continues he

Year	Place	Remarks
		<p>grows cold and his Pulse abates, till at last it is quite gone, and the Patient becomes almost as cold as a Stone, and continues in that State with a composed sedate Mind In this Condition he may perhaps live Twelve Hours without any sensible Pulse or Heat and then expire</p> <p>"Such were the symptoms and progress of this Fever in the Year 1715</p> <p>"Sometimes likewise the Patients burst out with bleeding at the <i>Anus</i>, and soon after die, and sometimes likewise at the Nose, by which means they have been relieved, but when the Blood issues from thence but in a few Drops, it is a bad Prognostic, and is generally the Harbinger of Death In most of these Cases the Patients are generally hot and dry, the Blood taken from them is very red, and scarce will coagulate, the Grume swimming upon the Surface of the Serum is a thin Leaf, having scarce any Consistence</p> <p>"The Patients have likewise often intolerable Pains in and about the Stomach, sometimes with those Pains they shall have a Liver and the plain Marks of a Sphacelus shall possess the greatest Part of the Abdomen before they die, particularly the Region of the Stomach and Liver It often also happens that the sick Person shall be almost stupid, and, being asked how he does, say, He is very well, at other times he labours under the greatest Agonies and Fits of Groanings</p> <p>"After Death the Corps of such appear livid in some Parts or other, or else marked with pestilential Spots, Carbuncles or Buboës I am of opinion that the Blood is from the Beginning full of putrid Alcaline Salts"</p>
1723	West Indies	In Jamaica, especially at Port Royal, and "very deadly after the inundation of the previous year"
"	Spain and Portugal England?	Several cities on the coast invaded At Lisbon the large number of patients with black vomit was specially noted The disease was attributed by Don Vincente Boibid, a celebrated physician of Madrid, to the "eating of fruit and drinking snow-water" The disease is said to have appeared in London, being transmitted from Lisbon
1724	Spain and Portugal	Uncertain whether a continuation of that just recorded, or a fresh introduction, again attributed to fruit and snow-water
1725	Mexico	At Vera Cruz, reported in Clavigero's <i>Histoire de la Mexique</i>

Year	Place	Remarks
1727	Spain	Five hundred of the garrison at Gibraltar died of yellow fever
1728	North and South America	Very fatal in Charleston, where it was termed 'bilious plague,' but a similar disease carried off great numbers of the population of Carthage and Portobello, in South America, the most fatal symptom was black vomit. The disease wrought great havoc among the crews of vessels under Don Domingo Justianini and of the galleons under Lopez Pintado
1729	West Indies	At Antigua
1730	America	Again at Carthage and Portobello
„	Spain and Europe	A formidable epidemic started at Cadiz, it was named 'el vómito negro', the infection was supposed to have been brought over from South America and, extending widely, continued its ravages until 1738. It is generally accepted that the 'pestilencia' starting in Cadiz was the first epidemic of yellow fever in Europe. During September and October 22,000 deaths took place after the arrival of the flotilla of Pintado from Carthage, where many of his men had died of 'el vómito prieto'. Bascome writing of this outbreak adds "It was probably this pestilence which during the seven years 1729-35 raged in Vienna, Pignerol, Fossano, Nizza, Rivoli, Asti, Lari, Acqui, Basle, Silesia, Thrasburg (Lower Rhine), Trino, Frésneuse (Lower Seine), Vimeux (Seine et Oise), Orleans (Loiret), Plouviers (Loiret), Meaux, Villeneuve, St George (Seine et Maine), Bohemia, Denmark, Sweden and Russia."
1731	West Indies	Domingo, brought there by the fleet coming from Portobello
1732	America	Raged in Charleston from May to October
1734	America	Ravaged in particular the cities of New York, Boston, Charleston, Philadelphia and Albany. It extended to the tribe of Mohican Indians and invaded the West Indies
„	West Indies	The same epidemic spread and caused a heavy mortality in Barbados
1735	West Indies	The French West Indies attacked, there was a severe epidemic in St Pierre, Guadeloupe. Also Domingo
1736	Spain	Outbreak at Cadiz
1737	America	Norfolk, Virginia
1739	America	Raged at Charleston from August onwards

Year	Place	Remarks
1740	West Indies	At San Domingo from June to December, and again the following year
1741	America	In South America among the seamen and troops under Admiral Vernon and General Whitworth It was reported that 8431 out of a total of 12,000 died of fever at Carthagena. The disease also occurred at Portobello, Panama and Vera Cruz In North America 240 deaths took place in Philadelphia, and there was an epidemic also at Norfolk, Virginia
„	West Indies	At Jamaica, in the English fleet coming from Carthagena, recorded by Hume in his <i>Account of the True Bilious or Yellow Fever</i> (published in 1778) and Williams in his <i>Essay on the Bilious Fever of Jamaica</i> (published in 1750)
„	Spain	At Malaga and Cartagena, introduced in ships en route to the West Indies from Africa or returning from the New World
1743	West Indies	At San Domingo in the summer and autumn; it continued with varying intensity for three years
„	America	At New York in the third quarter of the year, also at New Haven
1745	America	At New York and at Charleston
1747	America	Dysentery prevailed, especially at Hartford and New Haven This was succeeded by yellow fever which took a toll of victims for the next eight years Also in Philadelphia from June to October
1748	America	In Charleston from August to October
1750	West Indies	The French West Indies, Martinique, noted by Bally in <i>Du Typhus d'Amérique ou Fièvre jaune</i>
1751	West Africa and West Indies	Yellow fever of extreme malignity swept the West Indian Islands and the coast of Africa, as recorded by Lind who describes the mortality to have been produced by "a pestilential vapour which arose in the south-east of the Guinea Coast and traversed immense swamps" "In several towns, among the negro population the mortality was so great that there were not sufficient left to bury the dead and the gates at Cape Coast Castle were shut for want of sentinels to guard them, the whites suffering equally with the blacks from the fatal scourge" It occurred also in Senegal The above quotation from Bascome is interesting in show-

Year	Place	Remarks
		ing that the natives suffered severely, the place was not then an endemic site The Dutch West Indies was also attacked, an outbreak is recorded at Curaçao in April
1751	America	Particularly New York and Philadelphia.
1754	West Indies	Antigua in the autumn, noted by McKittrick in <i>De Febre Indoccidente maligna-flava</i>
1756	West Indies	Again at Antigua
1760	Dutch Guiana	Surinam Said by Fermin in his <i>Traite des Maladies les plus frequentes à Surinam</i> to be the first epidemic of yellow fever there Curaçao was also attacked again
1761	America	"Rife in North America in the summer and autumn"
"	West Indies	No details obtainable
1762	West Indies	At Havana, Cuba, 3000 sailors and 5000 soldiers were down with fever a month after landing They were the personnel of Count Albemarle's forces An expedition of English and Colonial Americans seized Cuba, but owing to the appalling amount of sickness they abandoned it after a few months
"	America	In Philadelphia from August to November
"	French Guiana	At Cayenne where the outbreak continued for three years
1764	America	In North America No details obtained
"	Spain	At Cadiz
1765	West Indies	Antigua, mentioned by Lind
1767	West Indies	St Lucia
1768	West Africa	At Senegal
1769	West Indies	Severe outbreak in Jamaica
"	West Africa	Continuance of the previous year's outbreak or a fresh one at Senegal
1770	West Indies	In Grenada
1771	Canary Islands	See remark on the outbreak in 1701, above
1778	America	The United States (Declaration of Independence, 4th July, 1776) After the British troops had vacated Philadelphia there was heavy mortality there from yellow fever
"	West Africa	Outbreak in St Louis, Senegal, in this and the following year This epidemic afforded the grounds for the classical description of the disease by Schotte, referred to (see p 310)
1779	West Indies	Bermuda attacked
1780	West Indies	Severe outbreak in Jamaica where there is said to have been 3500 deaths from yellow fever in four years

Year	Place	Remarks
1780	United States of America	In various parts but especially virulent in Philadelphia. This outbreak is particularly noteworthy, or perhaps we should say, this year should be particularly remembered because "a fever called 'break-bone fever' was also prevalent, but did not prove fatal." We now know that the same mosquito, <i>Aedes aegypti</i> , is the vector of dengue and yellow fever viruses.
1781	West Indies	In Havana and San Domingo
1783	America	In Baltimore
1786	West Indies	Prevalence of 'el vómito negro' at Havana
1791	America	Outbreak causing many deaths in New York, and 'bilious plague' raged in Philadelphia. Also New Orleans attacked where, says Drake, this was the first outbreak.
"	West Indies	Yellow fever at Havana, Cuba, and 'bilious plague' in Grenada.
"	French Guiana	Cayenne
1792	America	Very severe outbreak with great mortality in Charleston in July.
1793	America	Raged to an alarming extent in Philadelphia, resulting in the death of more than 4000 in the short period of four to five months, about one-tenth of the total population—all ages, all colours, rich and poor, clean and dirty. Community life was at a standstill, banks and factories closed. Dr. Rush noticed that 'moschetoës' were very plentiful. The outbreak subsided rapidly and "as mysteriously as it had started," with the coming of frost. There were many fatal cases also at Boston.
"	West Indies	Particularly Dominica where it is continued for three years. Also an outbreak in Grenada, believed to have been introduced by the ship <i>Hankey</i> which had come from Bulam. The infection was not regarded as "the malaria or 'yellow fever' [bilious remittent form of malaria, perhaps] of the West Indies, but as a new importation," hence the name Bulam fever. Other parts of the West Indies attacked were Trinidad, Tobago, St. Vincent, Barbados, Dominica, St. Thomas, Jamaica, Antigua and St. Kitts.
"	Venezuela	Caracas attacked in October.
"	British Guiana	Outbreak in Demerara.
1794	America	Prevalent in Baltimore. For the account of this outbreak we are indebted largely to a series of letters by Dr. Drysdale to Dr. Rush. Dr.

Year	Place	Remarks
		<p>Drysdale saw the first case at Bowley's Wharf, just before the patient died, on 7th August, and within a short period there were several more in the same locality. They were reported as bilious remittent fever, but soon became very numerous—one doctor visited over 120 in the day—and two physicians died out of five attacked. Another spot where cases were many was Fell's Point. Town cases seemed to be traceable to these two places. Investigation showed that these places were flat, low-lying, with unpaved streets, alleys dirty and ground swampy, houses had cellars containing stagnant water.</p> <p>Infection was probably introduced primarily from vessels from the West Indies which came up to the wharf, the captain of one had died on the voyage up, and on another, the <i>Triumph</i>, nearly all the crew were sick. "Locusts were not more numerous in the reign of Pharaoh than mosquitoes through the last few months." Infection was carried not only from ship to shore but also reciprocally from shore to ship. Dr Carroll mentions how one man "contracted the disease on shore and carried it on board the ship <i>Phoenix</i> whose crew was healthy. These all became infected and five out of twelve died."</p> <p>The disease prevailed also at Norfolk, Virginia [Bolduan in a letter to the <i>New York Times</i>, 3rd June, 1933, states that yellow fever was epidemic in New York thirteen times between 1791 and 1807 and that the city lost nearly one-tenth of its population in consequence].</p> <p>In 1794 it raged violently in New York, Philadelphia, Charleston, and other cities and continued on and off for the next six years.</p>
1795	West Indies	<p>At San Domingo (Haiti), "Yellow fever in all its fury." See William Fergusson's account (above, p. 295). Among European troops in a little more than four years some 700 commissioned officers and 30,000 soldiers died of it, and in the West Indies in 1794-5 "there died in the course of a few months not less than 6000 men." Other parts of the West Indies to be attacked this year were Grenada, St Vincent and Jamaica, and the French West Indies, Martinique and Guadeloupe, and the Danish island St Thomas.</p>
1796	West Indies	<p>In St Lucia 800 of the troops are reported to have died.</p>

YELLOW FEVER

Year	Place	Remarks
1796-97	America	<p>Prevailed at New York, Charleston, Boston, Newburyport, Philadelphia (where it caused 1292 deaths) and other States In 1797 it caused great mortality in Norfolk, Virginia, Providence, Portland and Savannah, and spread thence to New Orleans</p> <p>In Trinity Church, Salford, near Manchester, is a monument to the memory of Major Thomas Drinkwater, who died at sea on return from the West Indies in 1797 This contains the following verse</p> <p style="padding-left: 40px;">"Thrice had his foot Domingo's island prest, Midst horrid wars and fierce barbarian wiles, Thrice had his blood repell'd the yellow pest That stalks, gigantic, through the Western Isles!"</p> <p>Since one attack of yellow fever confers immunity for life, we must conclude that the diagnosis was wrong on at least two occasions, or else attribute the exaggeration to poetic licence</p>
,, 1798	Venezuela America	<p>At Guayra Trinidad was also attacked</p> <p>In the autumn of this year 'pestilential yellow fever' carried off many The citizens of New York (where 1500 deaths occurred among a population of 60,000 and sixteen doctors out of forty died), Philadelphia (3500 deaths), Wilmington, Newport, Albany, Boston, Portsmouth and New London suffered greatly from the disease [Possibly yellow fever was not alone responsible] There seems to have been some confusion in diagnosis, for Bascome states that patients "exhibited both bubo and carbuncle with many other symptoms of true plague Lake and marsh fevers prevailed also about this period in the low and swampy districts, such as Milford, etc This yellow pestilence was less generally characterized by inflammatory action and venesection was attended with less salutary effects than on former occasions"</p>
1799	America	<p>Again at Philadelphia, 1015 died from the disease In the third quarter of the year New Orleans, Charleston attacked and Norfolk, Virginia and Baltimore at the same time as Charleston</p>
,,(?)	West Indies	<p>The Bahamas, "at the end of the eighteenth century," soon after the erection of Fort Charlotte, near Nassau, "the whole of the 47th Regiment, men, women and children, were swept off by yellow fever in a few weeks"</p>

Year	Place	Remarks
1800	America	<p>Outbreak at Baltimore with high fatality rate. This is believed to have been the severest ever known in this city. The recorded deaths numbered 1197 out of a population of 60,000. As before it started at Fell's Point. The physicians were of opinion that it originated from the stagnation and putrefaction of filth and was not imported. No other details are available.</p>
,,	Spain	<p>The British fleet, with 18,000 troops on board, was visited off Cadiz by an epidemic disease, recorded by Boyle. At Cadiz in September and October 140-70 deaths occurred daily and in mid-September were numbering some 200. Infection spread to Xeres, Malaga and other parts of Spain. A fuller account by Burgoing makes it practically certain that the disease was yellow fever. He states "It was observed [at Cadiz] that most of those who were born in the West India Islands or in Spanish America escaped its influence, that it was not quite so dangerous to the old inhabitants as to those who had recently settled at Cadiz, and that the majority of foreigners fell victims to its fury."</p> <p>Between 12th August and 31st October it attacked 47,350 persons, and of these 7195 died, 'exclusive of the troops who had recently arrived for the defence of the coast, and who alone lost 3000 men.' Cadiz and other cities of Andalusia were not free from it till the end of the following April (1801). As stated above, terrible havoc was being caused in adjacent districts—Port St Mary, Isle de Leon, and Rotas—and infection extended to Chicklana, Puerto Real, St Lucar, Xeres, Seville, practically invading the whole of Andalusia. In Seville it is said that among a population of about 800,000 those attacked numbered 76,488, or 95 per mille, and in one month 14,685 died.</p> <p>The following preventive measures were put in force. Every dwelling or room where a case occurred was fumigated and whitewashed, the clothes and belongings of the infected were burned, and the dead were interred deeply and at a distance from the city. [We know from the work of Carroll, Reed and Lazear the reasons for these measures being ineffectual, for, as will be seen later, these investigators showed that</p>

Year	Place	Remarks
		the infection was not transmitted by a patient's clothes or effects, or by contact with dead bodies]
1800	British Guiana	In Demerara
"	Dutch Guiana	In Surinam
"	West Indies	Haiti A French army of Napoleon's picked troops landed, but in less than a year the mortality from fever, especially yellow fever, had been so great that the survivors withdrew, leaving the natives in possession
1801	America	Said to have been "prevalent in the United States", was present in Norfolk (August-October), New York (summer and autumn), Rhode Island (August-November), and sporadic cases in New Bedford, Massachusetts
"	West Indies	Martinique and St Martin (one of the Lesser Antilles) This is said to be the first record of any yellow fever in St Martin, it prevailed from July to November During the last four months of the year it was present in Jamaica
1802	French Guiana	In Cayenne and continued in the following year
"	Venezuela	In Caracas
"	America	According to Boyle yellow fever raged with much violence in Philadelphia The frequency with which New York and Philadelphia suffered is noteworthy, the reason is that the infection had by this time become endemic while the busy traffic entailed constant introduction of non-immunes
"	West Indies	The Bahamas Another outbreak at Fort Charlotte, Nassau, 220 died out of 300 of the 7th Fusiliers Also in the French West Indies and in Jamaica, Antigua, St Lucia
"	Spain	At Cadiz, probably introduced by vessels returning from Cuba
1803	America	Three thousand nine hundred deaths from yellow fever in Philadelphia In Boston small outbreaks occurred at the end of the eighteenth and beginning of the nineteenth centuries, but mostly limited to ships and the immediate neighbourhood
"	Spain	In Barcelona, infection being brought by vessels from Havana, and 1265 deaths occurred among 1739 cases treated, a fatality rate of 72.7 per cent In September the disease invaded Malaga, as recorded by Aregrila in his work on <i>The Epidemic Fever of Malaga</i> , and 6684 died among a population of 16,517

Year	Place	Remarks
1803	West Indies	The army of General Rochambeau was ravaged by it in San Domingo Fort Charlotte, Nassau, was again the scene of an outbreak with fatality higher than in the previous year—250 died among a garrison of 300 Fort Charlotte was now being spoken of as "The Abode of Death"
1804	Spain	In Andalusia Vómito negro broke out with great ferocity at Malaga and infection spread along the Mediterranean coast to Cartagena, Alicante, and even to the vicinity of Barcelona It caused many deaths in Gibraltar, where in October 120 deaths occurred daily Among a total population of 15,000 there died of yellow fever 4864 civilians and 869 soldiers It was present in Cadiz, but not so gravely The source of infection might have been either the West Indies, West Africa, or other Spanish ports—all were possible
,,	Italy	At Leghorn and Lucca
,,	West Indies	Especially at Martinique and Grenada
1805	Spain	Further outbreak at Cadiz
,,	America	At Philadelphia from July onwards
1807	America	In Charleston from August on
,,	West Indies	Jamaica attacked in the autumn Martinique in December and on into 1808
1810	Spain	Outbreaks recorded in Barcelona, Cadiz, Cartagena and Malaga Also in the Canary Islands
1811	America	New Orleans, Pensacola (Florida), Perth Amboy (New Jersey)
1813	Spain	During the last quarter of the year an outbreak in Gibraltar caused the death of many, both of soldiers and civilians
,,	West Indies	In Barbados, the disease continued or re-appeared in the three following years
1814	Spain	In the third quarter of the year, from August onwards, there occurred an epidemic which continued till October After this, yellow fever did "not appear on the Rock again for fourteen years"
,,	West Africa	In Senegal
1815	Mauritius	Boyle records "a disorder similar to the yellow fever" caused great mortality
1816	West Indies	In Antigua, reported by Boyle, also in Grenada, St Kitts, Martinique and Guadeloupe, also a severe epidemic started in St Thomas (Danish West Indies) in September and continued till January 1818
,,	West Africa	In Senegal, Sierra Leone and the Congo Coast

YELLOW FEVER

Year	Place	Remarks
1817	America	Great mortality from yellow fever at Savannah, New Orleans, Mobile, Natchez, Baltimore, Charleston and "various parts of the States"
"	West Indies	<p>Mortality from the disease among the troops stationed in Grenada was said to be 8 2 per cent Also outbreak in Dominica where the mortality was recorded as 29 per cent</p> <p>In Jamaica yellow fever was present in greater or less degree from 1817 to 1836, the mortality per thousand among the Whites was high (as recorded by Sir Rubert Boyce in <i>Health Progress and Administration in the West Indies</i>) At Montego Bay (probably at the present day one of the healthiest parts of the island) it was 150 7, at Spanish Town 141 1, at Up Park-Camp 121 0 Among the black troops the figure was about 10 per thousand</p>
1818	West Indies	<p>In Trinidad 30 per cent of the white troops died of yellow fever and in Tobago 13 per cent Also rife in Bermuda and British Guiana, continuing to prevail for the next two years It was very fatal in St Lucia where the mortality was 14 5 per cent, and among the troops in Grenada the mortality was 21 per cent Another outbreak occurred at Fort Charlotte, Nassau, forty deaths occurring in six months in the 15th Regiment</p>
"	America	<p>Said to have prevailed in the United States from 1818 to 1820 (no details) Also in South America, "in various parts", again no specific details are available</p>
1819	America	<p>Prevailed at New Orleans from May to the end of the year, in Mobile from June to December, in Charleston, in Baltimore where 191 cases were recorded, and "a few cases" in New York and Philadelphia</p> <p>The outbreak followed the arrival of an infected vessel from Cuba, the <i>Adventure</i> or the <i>Proserpine</i>, both with a cargo of coffee and the latter with hides also, as on former occasions the outbreak started at Fell's Point, in July, and continued till the end of October Many of the people moved away to healthier parts of the city, but too late, for many sickened and died there, though none of their relatives or friends was attacked [therefore, not locally infected and non-contagious] The disease spread to several ships tied up to the wharves whose crews were healthy, i.e. these vessels were invaded by infected and infective mosquitoes Dr David M Reese has given an</p>

Year	Place	Remarks
		interesting account of this in his <i>Observations on the Epidemic of 1819</i> Of 1016 cases reported all but twelve originated at the wharf area He notes that physicians making their visits by day escaped infection whereas those going there at night caught it—explained by the habits of the <i>Aedes</i> mosquito
1819	West Indies	In Tobago the mortality among the white troops was higher than in the preceding year, namely 18 per cent The disease also was present in Jamaica and Martinique
1820	West Indies	Very disastrous in Tobago, 80 per cent mortality being recorded among the white troops In Trinidad it continued from 1820 to 1825, with an average mortality of 3·2 per cent
„	British Guiana	In Demerara with a mortality of 16 per cent
„	America	At New Orleans from July to October, in Mobile from July to December, and in Philadelphia from July to November
1821	West Indies	Still present in Tobago, but clearly diminishing, the mortality being 25 per cent in place of 80 in the previous year Present also in Martinique and Guadeloupe
„	British Guiana	In Demerara with mortality 14 per cent
„	America	Appeared first in New York, but soon spread to Boston, Philadelphia, Baltimore, Charleston, New Orleans, Natchez, Mobile, Alabama, Havannah and along the banks of the Mississippi
„	Spain	Infection believed to have been brought by ships from Havana, Cuba, Barcelona, Xeres and Cadiz attacked In Barcelona it wrought great havoc, the population totalled 150,000, of these 70,000 remained in the port and 20,000 died of the disease The fatality rate is said to have been above 90 per cent, and at times 200–300 deaths occurred in a day At Xeres the British troops suffered severely, but the civilians more
1822	West Indies	Outbreak with high fatality in St Lucia and St Vincent
„	America	In New Orleans from September to November, Pensacola from July to November, and New York for the same period
1823	West Africa	Especially Sierra Leone
„	Portugal	Outbreak at Lisbon
„	South Atlantic	At Ascension Island, which lies 685 miles north-west of St Helena, and was occupied by the British in 1815

Year	Place	Remarks
1823	America	In Key West in August and September, and Natchez in August
„	West Indies	In Jamaica in the summer and autumn
1824	West Indies	St Lucia again attacked, mortality 21 per cent In Jamaica from August onwards
„	America	In New Orleans from July onwards, also in Charleston
1825	America	South America very deadly in Rio de Janeiro In the settlement of Aracaty 30,000 deaths took place "in a short time" In the United States in Natchez from August to November, and in Washington and Mobile in September
„	British Guiana	In Demerara
„	West Indies	At Guadeloupe in the French West Indies, and at the Danish island of St Thomas
„	West Africa	At Sierra Leone, as recorded by Boyle and Gore in the Army Medical Reports
1826	West Indies	French West Indies, Martinique and Guadeloupe both attacked
1827	West Indies	Outbreak in St Lucia
„	America	Walford records "Yellow fever prevalent in the United States," but gives no details Drake, however, mentions New Orleans as being attacked in July, and Mobile in August Also Pensacola in the summer Posey mentions Savannah, and Dickson and Porter Charleston
1828	West Indies	Trinidad, with a mortality of 13 per cent among the troops The infection was by this time probably endemic in Trinidad and a new consignment of troops had arrived, for in 1820-5 the mortality was only one fourth of that of 1828
„	America	In New Orleans from June onwards, and in Memphis from September to November
„	West Africa	In Senegal
„	Spain	In Gibraltar, which had been free from the disease, at least in epidemic form, since 1814, it broke out in September in the dirtiest and most thickly populated parts, but soon came to involve all classes and both military and civilians "It was observed to prevail to a greater extent and more severely in some situations than in others, particularly along the line of wall facing the sea—few of the soldiers stationed there escaping an attack"
1829	West Indies	In Havana, Cuba, and Jamaica

Year	Place	Remarks
1829	America	In New Orleans from July onwards, in Francisville in September, in Natchez, Mobile, Key West from August
„	West Africa	In Sierra Leone, reported by Boyle, Bryson, McDiarmid and Gore
1830	West Africa	Senegal again suffered
„	West Indies	Severe outbreak in St Lucia, with a mortality of 30.8 per cent, higher than in any outbreak previously recorded there
„	Colombia	At Ambelema, prevailed for five months and 1800 deaths are said to have occurred among a population of 4000
1834	America	This year and for the next quinquennium yellow fever prevailed in various parts of the United States, but especially at Charleston, which was crowded by strangers who were employed in rebuilding the city after its destruction by fire
1835	Dutch Guiana	Surinam attacked in December, the outbreak continuing into 1836
1837	Dutch Guiana	Surinam from May to July, possibly a recrudescence of the last outbreak, but as the town appears to have been free for fully a year, this may have been a fresh introduction
„	British Guiana	In Demerara ' This town was attacked during the following year also, but whether a continuation of this or from fresh introduction is not certain
„	West Indies	Havana, Cuba, and in Bermuda
„	America	New Orleans from July to October, Natchez from September to November and, at the same time, Mobile
„	West Africa	Another outbreak in Senegal
1838	West Indies	French islands of Martinique and Guadeloupe, and the British West Indies, Dominica and Trinidad
„	British Guiana	Demerara
„	America	Charleston from July to October
„	South Atlantic	Ascension Island Yellow fever broke out among the garrison and wrought much havoc The infection spread to the crews of several ships of war which touched at the island and many, both officers and seamen, died The disease was attributed to the effluvia arising from stagnant pools
1839	America	At Galveston, a port of Texas, also at Mobile, Charleston and Pensacola

YELLOW FEVER

Year	Place	Remarks
1839	West Indies	St Lucia Outbreak among the troops at Morne Fortune, of a complement of 134, there were 93 attacked and 20 died The disease appeared at St Vincent and Antigua
"	West Africa	Fernando Po
1840	British Guiana	Severe outbreak with mortality of 69 per cent among the white troops
"	West Africa	At Senegal
1841	America	Outbreak at Key West, Eastern Florida from June to August, at New Orleans from August to October, at Vicksburg from August to November, and Pensacola in August
"	West Africa	At Senegal, probably a continuation of the previous year's outbreak
"	British Guiana	At Demerara
"	Dutch Guiana	At Surinam
"	West Indies	In Dominica from June to September
1842	South America	Outbreak in Peru, no details available
"	West Indies	At Antigua from September to November
1843	America	Yellow fever appeared in a small inland settlement in Wilkinson County, Mississippi The circumstances were peculiar, according to Walford, it "could not have been imported, for it was not prevalent at New Orleans, nor at any place along the Mississippi River at the time The town itself occupied a healthy position, being situated on dry and well-drained ground" The disease prevailed also at Charleston, Mobile and Galveston (Texas) Another report states that it prevailed also at New Orleans, but whether before or after that in Wilkinson County is not mentioned If the former the source of the epidemic in the County is explained Probably, therefore, it was after, or Walford would not have spoken of the circumstances as being 'peculiar'
"	West Indies	In Bermuda from July to December
1844	West Africa	At Gorée, Senegal Some records give an outbreak in Senegal in 1845 and make no mention of 1844 Others, again, mention 1846 The disease was doubtless endemic in Senegal and newcomers would be attacked and according to the numbers these exacerbations might easily be recorded as separate outbreaks
1846	Mexico	At Vera Cruz the American invaders "died like flies" from yellow fever, says the report

Year	Place	Remarks
1846	America	In the plains of the United States "The Mormons, during their march from Nanvoo to Utah, suffered greatly from remittent and yellow fevers, and a scorbutic disease which they called the 'black canker' Their track across the desert was marked by the graves of those who perished" (Walford)
1847	America	Severe outbreak at New Orleans, between the 5th July and 22nd October 2544 died Also at Rodney, and at Vicksburg, Natchez and Mobile
"	West Indies	At Barbados in the last quarter of the year
1850	South America	In Rio de Janeiro, 4000 deaths occurred
"	West Indies	An outbreak began in the French West Indies this year and continued till 1853
"	French Guiana	At Cayenne Another, or, as some believe, a continuation of this was reported in the following year
1852	South America	Peru (no details)
"	America	At Charleston from August to November
"	West Indies	An epidemic appeared to begin at St Thomas, Danish West Indies, and then passed to Haiti, Martinique and Guadeloupe, thence on to Curaçao, Cuba, St Lucia, Barbados and Porto Rico
"	West Africa	Senegal and the Gold Coast, recorded by Sarouille in <i>De la Fièvre jaune épidémique dans les possessions françaises de la Côte d'Or</i>
1853	West Indies	Outbreaks continued in most of the places mentioned as foci in 1852 (v s) and also invaded the Coast of Mexico and the
"	America	Gulf Coast of North America and towns along the Mississippi valley New Orleans from May to October, also Vicksburg and Mobile, and the coast of Florida A Commission which investigated the epidemic of this year in New Orleans concluded that there was no ground for believing that the fever had been imported, but that it was of indigenous origin, resulting from local influences developed and intensified by peculiar atmospheric states
1854	South America	In Peru
"	Dutch Guiana	In Surinam
"	West Indies	Antigua Also at Curaçao
"	America	In the United States the following were attacked New Orleans, Mobile, Montgomery (Alabama), Savannah and Charleston

Year	Place	Remarks
1855	West Indies	Outbreak in the French West Indies in this and the ensuing two years
"	America	At Vicksburg and several places in Mississippi, Memphis (Tennessee), Norfolk (Virginia)
"	French Guiana	At Cayenne and continued in the following years till 1858
1856	West Indies	Martinique and Guadeloupe (French West Indies), St Thomas (Danish W I), Jamaica and Bermuda
"	America	At New Orleans from July onwards, Charleston from July to September, New York from July to September, Long Island in July and August
1858	West Indies	In Antigua, St Thomas, Trinidad Also in Panama
"	America	In New Orleans, Mobile, Charleston, and a few imported cases were reported in Philadelphia
"	West Africa	In Senegal and in Gorée (Senegambia)
1859	West Africa	In Sierra Leone and Senegambia, at Gorée and Bathurst
1860	Honduras	At Belize
"	West Indies	Cuba, Jamaica, the Windward Islands, and in Haiti and Martinique
"	West Africa	At Macarthy's Island (Gambia) and Loanda, Angola (Congo)
1861	Europe	Small number of cases in France, infection being brought on a vessel from the West Indies and limited to the ship itself and those who worked on it or visited it
"	Colombia	At Cartagena
"	West Indies	The Bahamas (Nassau), Martinique and St. Thomas
1862	West Africa	Sierra Leone, Gold Coast (reported by Sarouille), Calabar, the Benin Coast, the Congo Coast, and Fernando Po
"	West Indies	Cuba, Tortuga, St Thomas, Bahamas, Barbados
"	Canary Islands	Probably introduced there from West Africa, the Canaries being a port of call between Africa and Spain and Portugal
1863	West Africa	Outbreak in Senegal, after an absence—at least absence of any record—for the past five years
"	America	In the United States, an outbreak at Pensacola from July this year to the following May Also in Mexico, Tampico
1864	West Indies	Bermuda from June to December
"	West Africa	Lagos (Sierra Leone, now Nigeria)
1865	West Africa	Sierre Leone and Loanda (Congo Coast)

Year	Place	Remarks
1865	Britain	Swansea, Glamorganshire Brought by the <i>Hecla</i> from Cuba, Customs Officers and men working on the ship were attacked and three of the crew of a vessel lying alongside the <i>Hecla</i> , twenty persons in all (see p 290)
,,	West Indies	French West Indies, Guadeloupe, and Haiti
,,	Mexico	At Campeche
1866	West Africa	At Senegal, continued into the following year, Gorée, Bathurst, Senegambia, recorded by Ledout in <i>Archiv de Med navale</i> , 1868 Also outbreak in Sierra Leone
,,	West Indies	Jamaica, British W I, and St Thomas, Danish W I
1867	West Indies	Cuba and Barbados, and the Pacific Coast of Panama
,,	America	In Galveston and several places in Texas, New Orleans from June to November, Vicksburg, Mobile, and Key West from August onwards, also at Pensacola and Philadelphia
1868	Mexico	At Manzanillo
,,	Central America	San Salvador, Nicaragua
,,	West Indies	St Kitts, British W I, Martinique and Guadeloupe, French W I, and Cuba where the outbreak continued to 1870
1869	America	In Peru, South America
,,	Venezuela	Caracas
,,	West Indies	At Nassau and Trinidad
1870	America	United States, the last recorded outbreak of yellow fever in New York.
1872	West Africa	Senegal, this time the infection penetrated into the interior to Gorée and to St Louis and Batul, following the trade routes
1873	America	Widely prevalent in the Southern United States, in Texas, in New Orleans, in Memphis (Tennessee), Montgomery and elsewhere in Alabama, and Vicksburg, Mississippi
1875	Mexico	Severe outbreak reported by Heinemann in Virchow's Archives, 1879
1877	West Indies	Jamaica
,,	French Guiana	At Cayenne
1878	America	At New Orleans where 4046 deaths occurred and the disease spread along the Mississippi as far as Southern Illinois
,,	Mexico	Severe outbreak recorded by Heinemann
1879	America	Outbreak at Memphis on the Mississippi

YELLOW FEVER

Year	Place	Remarks
1881	West Indies	Barbados, after this the island was free for a quarter of a century. A few cases were reported from Grenada.
„	British Guiana	The last epidemic recorded here.
1883	Colombia	At Cucutá in the Department of Santander del Norte continued for nine months, 213 fatal cases were reported, according to Martínez Sáenz and Cuervo Márquez.
1886	Colombia	Again at Cucutá, during the five months' epidemic 290 deaths took place from this disease (Sáenz and Márquez). Also at Escobal, where among a population of 200 there were sixty dying of yellow fever.
1887	West Indies	Outbreak in the French West Indies, Martinique and Guadeloupe, in this and the succeeding year.
„	Colombia	At Cucutá. The number of cases is not recorded, but Sáenz and Márquez state that the outbreak prevailed for two months and that the fatality was 70 per cent. This seems very high, unless there had been an influx of non-immunes, for the disease had been present in epidemic form in Cucutá the previous year and in 1883 (v s).
1888	Canary Islands	
„	Colombia	At Ocaña in Santander del Norte. The outbreak continued for eight months, and among a population of 12,000 there were 400 deaths due to it (Escobar).
1889	West Indies	Trinidad and Tobago.
„	Colombia	At Barranquilla, Atlántico Department. Dr A. Pantoja does not mention the number of cases but states that the 'mortality' (? case mortality) was 23 per cent.
1891	West Indies	Again in Trinidad.
1894	South America	Severe outbreak in Brazil; 5000 deaths were recorded in Rio de Janeiro.
„	West Indies	Trinidad (see below, 1907).
1895	West Indies	Disease again appeared and became epidemic in the French West Indies. Towards the end of the century there was considerable loss among the American soldiers before Santiago, Cuba, and the Spaniards also found yellow fever a formidable ally of the revolutionaries when they attempted to subdue the Cuban insurrection.
1900	West Africa	Started in Senegal and spread along the railway from Kayes to Dioubéba in the Sudan, 1901. Dakar was almost decimated.

Year	Place	Remarks
1900	Colombia	Ocaña, Rosario, San Cayetano and El Carmen, all places in Santander del Norte, were attacked, but no details are obtainable <i>Aedes aegypti</i> , however, is very scarce and the cases may have been of the rural type
1901	West Indies	Cases reported from St Lucia, ascribed to engineering works and excavations being carried out for construction of a railway
1902	Dutch Guiana	In Surinam (see below, 1908 epidemic)
1905	America	Outbreak in New Orleans The first in more than a quarter of a century in the United States, the preceding being that at Memphis in 1879
1907	West Indies	<p>Small outbreak in Trinidad Five cases in the first quarter of the year, all the patients were new arrivals The type was severe, 4 of those attacked died By August there had been 38 cases and by the following March 47, of which 28 proved fatal</p> <p>It is thought that introduction may have been from Venezuela, or that intercommunication between Venezuela and Trinidad and the previous epidemics in the latter (1889, 1891, 1894) had made Trinidad an endemic focus Two cases were seen in Grenada, but they had been imported from Trinidad and as they were promptly dealt with no secondary cases occurred</p> <p>The wide extent of this epidemic was attributed to the unwillingness or inability on the part of physicians to diagnose and notify mild cases Very likely the former, for comparatively recently, in 1905, a physician in a large city of Texas remarked to Dr Carroll "We never report our cases of yellow fever until we have about a dozen of them" In the New Orleans outbreak many of the physicians, even those of repute, would not report a case unless black vomit was observed</p>
	West Indies	Barbados There had been an interval of twenty years since the previous outbreak This one started in November in Bridgetown and by February had spread to other parishes A hundred cases were recorded, more than half were blacks, indicating fresh introduction Many early cases were missed, and there was no little opposition to those who ventured to make the diagnosis The source whence the infection was imported into Barbados has been discussed (see p 297) The outbreak lasted till 1909

YELLOW FEVER

Year	Place	Remarks
1907	Colombia	Cases at Cucutá (Santander del Norte) and Buena Ventura (Valle) At the former <i>Aedes aegypti</i> is very scarce—Kerr and Patiño failed to find them—and as no other details are available we incline to the belief that in Cucuta the cases were of the rural type of the disease
1908	South America	Venezuela
„	Dutch Guiana	In Surinam It is thought by those resident in Surinam that the disease exists there endemically and flares up with incursion of susceptibles This opinion is based on a study of the 1902 and 1908 epidemics, on the grounds that (1) they coincided with the advent of a large number of non-immunes, (2) the course was typical in these persons and ended fatally only among them, (3) Europeans and other Whites who had been some years in the country were immune or had merely abortive attacks, (4) whites born in the country, but who had left it for years and came back might contract the disease in a severe form and even die of it
„	West Indies	Sharp epidemic in the French West Indies, Martinique, from June onwards Though no actual outbreak of an epidemic character had been seen in the French West Indies since 1895, suspicious cases had occurred, and the outbreak of 1908 was thought to be of local origin, starting in Fort de France, and spreading all over the island Among the natives there had been many attacked by 'inflammatory fever,' the character of which had been completely misunderstood until more recently arrived non-immunes began to suffer Within twelve months from February 208 cases were reported, and, as many more were attacked and in children the course was very mild, it is thought that the actual number of cases was not far short of a thousand
1910	Colombia	At Bucaramanga, Piedecuesta, Florida, Girón and San Vicente de Chucurú, all in Santander Department, in all but the first named it persisted into 1912 No details are available as to the number of cases <i>Aedes aegypti</i> was not found in the first three townships and in the other two they were present in small numbers only The outbreak may, therefore, have been of the jungle or the rural type At other times the <i>aegypti</i> index may be high in Bucaramanga, in 1923 it was 86 per cent, in 1932 it again was nil
1912	South America	Venezuela Nine cases reported in Caracas

Year	Place	Remarks
1912	Colombia	At Barranquilla (Atlantico) and Cartagena (Bolívar)
1914	South America	Outbreaks in Maracay district of Venezuela, preceded by deaths of red howler monkeys (<i>Myctes seniculus</i> , one of the Cebidæ) This is the first suggestion that these animals might be a possible source of infection
1915	Colombia	Buenaventura, Cali, and Caldas attacked, all in Valle Department
1917	South America	In Maracaibo, Venezuela
1918	South America	Eight cases reported from Coro, east of Maracaibo
1920	Colombia	Buenaventura (Valle)
1923-27	West Africa	Yellow fever again becoming active in the Gold Coast, 22 cases being notified In 1924 13, and in 1925 there were 10 in the Gold Coast and 21 in Nigeria In 1926 there were 27 in the former and 11 in the latter In 1927 only 2 cases were notified in Nigeria, but by the end of October there had been 107 in the Gold Coast, 41 fatal, and the disease was known to be present in at least 10 large towns During the same period there was an epidemic in Senegal (see below) and cases were also notified in the French Sudan, the Ivory Coast, Dahomey, Togoland and the Upper Volta, and by the end of 1927 the Belgian Congo, Mahadi being declared infected in January 1928
1926	West Africa	Since the epidemic of 1900 which wrought so great havoc at Dakar there seems to have been a lull for a quarter of a century in this part of West Africa In the last three months of 1926 cases became more frequent in Senegal and an extensive outbreak occurred This last has been already referred to (see p 306)
1928-29	South America	Venezuela, in the Cuyuni River Valley Outbreaks in several towns El Callao, Curi, El Palmar and Guasipati In the last there were 149 cases, five of them fatal Clinically the course was mild and in many the symptoms were such as to give rise merely to suspicion, but pathological changes and serological tests confirmed the diagnosis These facts suggest that this region is a silent endemic focus of yellow fever, or perhaps the 'jungle' rural type invading the towns
1929	Colombia	At Socorro and Guadalupe in Santander Department No details
1932	West Africa	French Guinea A severe outbreak in three districts with a total of 8600 cases and 1540

YELLOW FEVER

Year	Place	Remarks
1936	South America	<p>deaths in three months. The epidemic was thought to be "influenza without pulmonary symptoms," but the results of protection tests supported the diagnosis of yellow fever.</p> <p>The interest of this outbreak which occurred in Paran�, in the Santa Rita district of the town of Cambar�, from February to April, consists in its being an outbreak of the ordinary urban type originating from a case of infection contracted in the jungle. The disease in the town was limited to nine houses in an <i>Aedes</i> infested area of ninety metres diameter. There were 47 inhabitants of these houses, and 25 of them were attacked.</p> <p>A labourer had, for three weeks prior to his attack, worked daily sixteen kilometres from Cambar�. He was taken ill on 10th February, and the diagnosis of yellow fever was confirmed by a positive protection test in July. Through out his illness he lived in one of the nine houses, to which he had been brought. His place of work was primeval jungle, nine timber-cutters worked there and all were ill with fever between February and mid-March, and the blood of five of them was positive for yellow fever in July. They did not live in nor visit Cambar� town or any place where yellow fever was known. The first urban patient was taken ill on 27th February, seventeen days from the beginning of the illness of the man infected in the jungle. The house to which this man was brought and that where the first 'urban' patient lived were in the same small yard and ten metres distant from one another. Three days later another case developed in the first (rural) patient's house and a third in the house next to his, thereafter twenty cases had occurred by the 12th April. The local outbreak was stopped by the usual anti-mosquito measures. One hundred and eight samples of blood were taken from inhabitants of Cambar� beyond the limits of Villa Santa Rita, but none gave the protection test.</p>

The foregoing table deals only with mosquito-borne yellow fever transmitted by *A des  gypti*. The subject of Jungle Yellow Fever is treated in a separate section.

4 THE MODE OF INFECTION

In the days when the diagnosis of yellow fever was uncertain, when the disease was not clinically differentiated from bilious

remittent malaria, from 'malignant pestilential fever,' typhus and others, ideas as to the way in which infection was contracted were of necessity vague. So little was really known of its nature Moseley in his *Treatise on Tropical Disease* relates that two physicians of Kingston, Jamaica, Drs Williams and Bennet, disputed so hotly as to whether yellow fever was an 'inflammatory disease' or not that they fought a duel about it on 29th December, 1750, which resulted in the death of both combatants, and left the question no nearer decision.

The facts as known led rather to generalization, as that the disease never originated in country districts [jungle yellow fever in the absence of *Aedes ægypti* is recent knowledge], required a certain density of population, on the sea-coast or at large estuaries. The *materies morbi* haunted the seaports and only slowly extended beyond them. Its origin and spread were said, quite rightly, to be favoured by the congregation of persons born in a cold climate, we should say nowadays by the influx of non-immunes. Others regarded concomitant insanitary conditions as ætiological, but clearly the writers were not convinced, for when referring to them as causes they show by the tone of their writing a sceptical reservation. It was said to be a disease of cities connected with putrefying, fæcal matter, overcrowding and filth generally. Thus, in Buenos Aires, "the streets are narrow and ill-ventilated and the foundations of some of the roads consist of offal. The closets are excessively filthy and the houses overcrowded," and yellow fever was severe there. Nevertheless—and here we see the reservation and the influence of the early bacterial era—"the centres of infection were always on seaboard, often at the mouths of great rivers," and "it is supposed that the special microbe exists in its free state in the brackish marshes formed in their estuaries." We shall return to the microbe theory again shortly.

In Florida conditions were thought to be very favourable for "the growth of yellow fever" because the streets were blocked by heaps of decaying garbage of all sorts, drains were obstructed and the yards encumbered with refuse, the town was flat and low-lying, with no effective drainage and the adjacent pine forests were interspersed with marshes and alluvial basins. "In India the product [of such conditions] would not be yellow fever but malaria, which is in firm possession of the Eastern world."

Direct transmission from sick to healthy was disproved as long ago as 1793 when Firth, a physician of Philadelphia, inoculated himself, injecting into his arm blood from a yellow fever patient and, heroic man, drank some black vomit [!] without ill

effects, at all events without contracting the disease. The inoculation must have been from a patient later than the third day of illness, for the blood is infective till then at least. Blair (1850) also brings forward evidence to disprove infection by contact, noting that the wives of yellow fever patients, although sleeping in the same bed as their infected husbands, did not contract the disease, nor did another person who was placed in the bed recently occupied by a fatal case of yellow fever.

The British Commission of 1852 noted that epidemics were often local, but that others, in spreading, might skip over certain districts, rigid seclusion of patients in an epidemic they found afforded no protection and they decided, in consequence, that yellow fever was not contagious.

We have already referred to Blair's points for differentiating malaria from yellow fever ætiologically (p. 311), that either might occur independently of the other—explicable now in part by the knowledge of the differences in life-histories between *Anopheles* and *Aedes*, the former being an 'earth-pool breeder,' the latter preferring domestic receptacles, drinking-water barrels and such-like.

Hastings, in his book *Lectures on Yellow Fever*, mentions Stephens's views as to there being "three yellow fevers" in the western hemisphere—one caused by excessive heat and not contagious, one due to heat and malaria combined, and a third contagious, caused by emanations from the bodies of those attacked. Hastings considers this question and concludes that he is "perfectly satisfied that there is but one cause," namely, malaria or exhalations from alluvial marshy soil which is subject to periodic inundations and draining. He is very dogmatic and states that the disease is always confined to districts of drying marshes. "Indeed," he says, "there is so little difficulty in the subject that, in the past season, the disease was predicted at the city of Tabasco, an alluvial marshy situation, eighty miles in the interior of Mexico." He could find no grounds for it being contagious, he had slept under the same roof as yellow fever patients, and been in close contact with them from the first day of illness till the fatal termination, had "cut himself with a scalpel when handling black vomit" and other fluids post mortem, without any ill effects.

As in the case of malaria, so in the history of elucidation of the cause of yellow fever there is a bacillary or organismal phase. Professor Harrison and the Rev. Sutton Morley in Barbados took samples of mould from graves of yellow fever patients and inocu-

lated it into small animals and found it non-infectious. One would not think that any important conclusion could be drawn from such a useless test, but they suggested that

The theory that we believe . . . to be the most reasonable and that, if not actually accepted now, will be . . . is that yellow fever is a highly contagious disease, but that the germs, whatever they may be, require some time and suitable opportunity for their development before they can reproduce themselves in another body, and that thus the disease is not at least generally communicable from a sick person to another who may be in ever so close proximity to him

Another wrote in the latter half of the nineteenth century

The true method of propagation would seem to be this. The cause is a particular microbe, which thrives in tidal ways or mudbanks, or in the warm moist soil only slightly raised above sea-level, and especially when filth from human habitations is allowed to decompose. Possibly a brackish or slightly saline ground is best adapted for its growth. A certain temperature and moisture cause it to multiply and emanate from these situations in large quantities

As with malaria, so with yellow fever, turning the soil in construction works was held to be not merely a possible but a likely and potent cause. This was a common belief up the last years of the nineteenth century. The authorities of Charleston, Mobile and other cities in America passed special ordinances prohibiting turning up of the soil during certain seasons of the year.

Izett Anderson as recently as 1898 supported this view and quoted as evidence that in Kingston, Jamaica, between 1872 and 1897 the soil had been "extensively turned up on three occasions" in 1872-3 for laying new water-pipes, in 1876 for laying gas-pipes, in 1897 when a drainage system was installed. *On each of these occasions, he states, there was a severe outbreak of yellow fever.* Anderson, however, in his discussion of the diagnosis confuses yellow fever with bilious remittent and other forms of malaria.

Dr Freire claimed that by injection of attenuated 'yellow fever microbes' he had reduced the mortality of the disease by 90 per cent and states that he bases his conclusions on 10,524 vaccinated persons. This organism was a micrococcus, 0.6-0.7 micron in diameter, present in the kidney, spleen and liver of patients, where they agglomerate and greatly distend the blood-vessels.

Another organism which for a time was raised to ætiological rank was the *Bacillus icteroides*, isolated in 1897 by Sanarelli. When injected into dogs it was reported to cause the symptoms and the lesions resembling those of yellow fever. These claims

were investigated by members of the American Commission in Cuba in 1900—Reed, Carroll, Lazear, Agramonte among them—but it was found that the blood of yellow fever patients did not contain it although such blood was infective, that it could not be recovered from the tissues of fatal cases, and finally that it was closely related to the hog-cholera bacterium. Whether this was the same as the *Bacillus* of Sternberg, which also for a time held the field, we cannot say, but the Commission agreed with Sternberg who had expressed scepticism of *B. ictteroides* as the cause and turned to a more intensive investigation of mosquito transmission (see below). Dr Sternberg, however, believed that infection could be transported in cargo and effects, for he stated that it was brought to Fort Barrancas from New Orleans in a barrel of potatoes and that several instances were on record of infection from the clothes and other effects of persons dead of the disease.

To explain the escape of the majority of the indigenous population when an outbreak occurred three reasons were adduced. First, selection—certain persons being insusceptible and so surviving, second, natural acclimatization or imperceptible vaccination, third, a previous attack—a shrewd guess—in consequence of which the microbe could not flourish effectually among a population unless there were numbers of strangers present, or the disease had been absent so long that people had grown up unattacked (also found later to be true). It was believed, however, that once started the fever could spread by inhalation of the organisms from the soil and by direct infection from sick to healthy. The argument was, it seems to us, weakened rather than supported by the statement that

ordinary malarial fever may differ greatly from yellow fever and from influenza in the clinical aspect, but conditions largely similar may give rise to each, just as many different kinds of microbe may grow well on boiled potato

—not a very happy simile

Dr Creighton in his *History of Epidemics in Britain* 1891, also clings to the idea of microbe and soil contamination. He suggests that the slave-ships from Africa, crowded with negroes and subject to hideous conditions of filth and disease, especially dysentery, may have led to the production of the yellow fever which attacked the whites and spared the negroes.

The ports of debarkation of the slave-trade became the epidemic seats of yellow fever. The theory is, that the matters productive of yellow fever were brought to the West Indian harbours, deposited

there, left to ferment and accumulate, and so to taint the soil, the mud and the water and to become an enduring source of poisonous miasmata

Again—

The ships' bilges would be foul beyond measure, it was just the contents of the bilges that would be pumped or thrown out when the ship was moored in the harbour or careened on the mud

The careenage at the head of the bay was the regular receptacle of the ordure of slave-ships year after year. Yellow fever is a fever of only a few *inhabited* spots, and the steady seats of it are all harbours at some time distinguished as the resort of slave-ships. Everything points to its being a poison lurking in the mud or even in the water of the slave-ports, and in the soil of their foreshores, wharves, and houses along the beach. The poison entered the bilges of ships moored in the harbour, and rose from the holds as a noxious vapour to infect the crews. The periodic epidemics of yellow fever are apt to occur when the ground is unusually dry, subsoil water low, and the pores of the ground filled with air to an unusual extent. Yellow fever may almost be described as a typhus of the soil. It has its habitat in the soil, like plague and like cholera, and it depends largely on the state (level) of the ground water.

The following sums up the general ideas on the subject in the eighteen-seventies

1 In the Western Hemisphere certain poison germs originate spontaneously in most if not all the West India Islands, at least as far north as New Providence, Bahamas

2 Such germs, if not exposed to a temperature below 32° F, or to the chemical action of certain agents, may remain virulent but dormant for an unknown length of time in the holds of ships, in stores, clothing, bedding, decaying animal or vegetable matter or soil containing such. Under favourable conditions of temperature and moisture they become active

3 Owing to these germs being so widely distributed and able to retain their potency for a long time, exclusion by quarantine is not practicable

4 Immunity of a country can only be attained by thorough sanitation, including disinfection of ships, their holds and cargo, and the effects of the passengers and crew, isolation of each case, precautions on land, especially in seaport towns, such as cleaning up the streets and yards and avoiding overcrowding, and draining low-lying marshy land

In 1848 Dr Josiah Clark Nott, of Mobile, Alabama, published some work on yellow fever, upheld the mosquito origin or trans-

mission and surmised that the mosquito of the lowlands might be the origin of malaria fever. This is the first reference we have been able to discover suggesting any connection between yellow fever and mosquitoes. Five years later, in 1853, Louis Daniel Beaupérthuy affirmed that yellow fever was due to the same cause as intermittent fever, and that yellow fever develops under conditions which favour multiplication of mosquitoes, that remittent, intermittent and pernicious forms are due to an animal or vegeto-animal virus introduced into the human body by inoculation. We see here that Beaupérthuy confused malaria and yellow fever, but it is right to add that by the term 'pernicious forms' he was not speaking of the *accès pernicious*, applied by the modern French writers to cerebral, algid, dysenteric, choleraic and other grave symptoms in occasional cases of subtertian malaria, but of yellow fever.

Beaupérthuy made many shrewd observations, as is seen by perusal of papers published after his death in 1871, by his brother. It is clear that he thought the infection was carried by the mosquito, but that the virus was telluric, obtained by the mosquito feeding on decomposing matter, though, he states, "marshes are not unhealthy from putrescence of water, but from the presence of mosquitoes." That man himself might be the source of infection does not seem to have presented itself to him as a possibility. To quote his own words, first as regards malaria and then as regards yellow fever:

Les fièvres intermittentes sont graves en raison du développement des insectes tipulaires, et ces fièvres cessent d'exister ou perdent beaucoup de leur intensité dans les forêts qui par suite de leur altitude nourrissent peu de ces insectes, quelles que soient les masses de matières végétales qui y subissent la décomposition putride.

And, with regard to yellow fever

Les causes de cette maladie se développent dans les conditions climatiques leur permettant de s'étendre à la fois ou successivement sur plusieurs localités. Ces conditions sont l'élévation de la température, l'humidité, le voisinage des cours d'eau, les lagunes, le peu d'élévation du sol au-dessus du niveau de la mer. Ces conditions sont celles qui favorisent le développement des insectes tipulaires.

In 1881 Carlos Finlay—his father was Scottish and his mother French, but he was born in Cuba and baptized Carlos Juan—presented a paper at the session of the Academy of Sciences Havana, on the 14th August suggesting that the mosquito carried infection from *man to man*. Finlay has not received all the credit that is his due. He enunciated his theory of an intermediary

transmitting agent of yellow fever and went so far as to suggest a mosquito which had "on the corselet a combination of lines in the figure of a two-stringed lyre" and was denominated *Culex fasciatus*. This was nearly twenty years before Reed, Carroll and their co-workers took up a detailed investigation of the problem. He found by experiment that the disease was transmissible by the bite of a mosquito in the early days of the illness [he had no idea of the period of development in the mosquito and the period during which it was non-infective]—he thought up to the fifth day.

Finlay wrote and published many articles on the subject, we may mention four of special importance. First, that presented to the Havana Academy of Sciences in August 1881, referred to above, it was entitled "El mosquito hipoteticamente considerado como agente de transmisión de la fiebre amarilla." Second, "Patogenia de la fiebre amarilla," published the following year and critically reviewed by A. Corré in *Archives de Médecine navale*, Paris, 1883, in a paper "Revue critique sur une nouvelle théorie pathogénique de la fièvre jaune." Third, in English and under the anglicized name Charles Finlay, "Yellow Fever Its Transmission by Means of the *Culex* Mosquito?" in the *American Journal of Medical Science*, Philadelphia, 1886. The fourth is a paper referred to by Professor Nuttall, entitled "Les Moustiques et la fièvre jaune," *Rev Scientifique*, 1887. This is not mentioned in the list of ninety articles on yellow fever given in a book on Finlay's life and work, with reprints of many of his selected papers, given to the author by his son, George H. Finlay.

Finlay considered that immunity to the disease might be effected by allowing a mosquito to bite a healthy subject after it had sucked the blood of a yellow fever patient. Between 1883 and 1890 he inoculated, as he called it, in this way thirty-three Jesuit and Carmelite Fathers who came to Cuba, thirty-two others being left to serve as controls. Five of the controls died of yellow fever, but none of the former, inoculated, group. According to Finlay, inoculation by one or two thus recently contaminated mosquitoes is free from danger and in 18 per cent a mild attack follows resulting in immunity.

The experiment was not free from fallacies, all the sixty-five may not have been bitten subsequently by infective mosquitoes, also the inoculated were lucky in that the dose injected was, being direct, probably quite small and there being only a brief interval the virus had not had time to develop in the mosquito, for it is probable that a single fully infective mosquito can convey the

disease Perhaps, also, some of the patients on whom the mosquitoes had fed were beyond the third or fourth day of their illness, that is, had passed the infective period

We have seen that to Nott of Alabama is due the credit of first suggesting the connection ætiologically between mosquitoes and yellow fever and how Beauverthuy five years later announced that the disease was propagated, he probably meant transmitted, by the "house-haunting mosquito" To Finlay of Havana is due the honour of being the first to make direct experiments to prove this He further came to the conclusion that the chances of ill resulting from allowing *Aedes* to bite man after feeding on an infected patient were but small, 18 per cent among ninety persons so inoculated suffering from the fever "in a very benign form," and we have shown how fortunate he was in not killing them all, as he might have done, had he kept the infected mosquitoes for twelve or more days instead of two to four

Finlay published his results, but the seed fell on rather barren and dry ground, and he was regarded as a mere theorizer, if not an actual crank—the lot of many a scientific pioneer

In spite of the writings of Nott in 1848, of Beauverthuy in 1853 onwards, and of Finlay from 1881 repeatedly in the next ten years, a report written in 1892 states

This semi-malarious disease arises like cholera from dirty, damp soil, ships, etc., to which the germs had at some previous time been brought The places where it is acclimatized are not very many, and it is sensible to cold, so that with proper cleansing measures, quarantine and prevention of overcrowding, it could be rapidly reduced It is at present terribly destructive at several Brazilian ports and eighteen English captains have died at one port within a few months

Nearly twenty years after Finlay read his first paper in Havana before the Academy of Sciences in 1881, American soldiers were dying in enormous numbers from yellow fever A Commission, with Major Walter Reed as head, and James Carroll, Jesse Lazear and Aristides Agramonte as members, was sent to Quemados to undertake an intensive investigation into the subject Three years before Sanarelli had isolated the organism which he named *B. icteroides* (see p 353) and claimed to be the causative agent This at the time held the field and the Commission naturally and rightly began by testing this claim Their findings have been recorded above, they were negative and the members turned next to consider Finlay's mosquito theory

We need not describe in much detail the experiments they devised and carried out, but they must be summarized One

point seemed very puzzling and, at the time, difficult to explain. A patient would be attacked and might die, or might recover and go away convalescent (for recovery from yellow fever may be remarkably rapid). Without any reintroduction of infection, without any contact with another case outside, one or more inmates of the same house would in a fortnight or so fall sick with the disease. The Commission inferred that, if the history was correct that there had been no contact with patients outside and no fresh introduction of infection, then, if the mosquito theory were to hold good, it would seem that time was necessary for the virus, whatever its nature, to grow in the insect.

That the mosquito could transmit infection was proved in the case of Carroll, one of the members of the Commission, for he was bitten by an experimental mosquito on 27th August, on the 29th he complained of feeling ill and by the 31st was very ill, but fortunately made a good recovery. Lazear was less fortunate, while he was going on his round in the wards a *Stegomyia* (*Aedes*) mosquito settled on his hand. He left it undisturbed to bite. This was on the 13th September, five days later he became very ill and died a week after, on the 25th September.

There are others who should not be considered by posterity as merely 'unknown warriors', it is only right that their names should be handed down to history as heroic volunteers, for they submitted themselves to experiment, knowing well—and thus showing true courage of the highest order—that death was lying in wait for them. They were Private William H. Dean of Grand Rapids, Michigan, Private John R. Kissinger of Ohio, and John J. Moran, a civilian clerk in General Fitzhugh Lee's office, who were bitten by experimentally infected mosquitoes, but recovered.

This, of course, proved that yellow fever could be transmitted by infected mosquitoes, but it was necessary to test whether the disease might be conveyed in any other way.

For this purpose they had a small house built at Camp Lazear, 14 feet by 20 feet, whose interior was maintained at a temperature of 90° F and the air kept moist—the conditions, in short, under which yellow fever flourished—but with mosquitoes excluded. The objective was to test the old idea that infection might be conveyed directly from the clothing and effects of yellow fever patients. The room having been prepared, Dr R. P. Cooke [or Cook, the name is sometimes spelt one way, sometimes the other] and six privates of the hospital corps—all honour to them!—entered and lay in the beds in which patients had slept who died of yellow fever, using their unwashed sheets and blankets and

pillows which had been soiled by *vomito negro*. There they stayed for twenty nights, a time well over the incubation period of the disease, but none of them became infected or suffered in health in any way. The two soldier volunteers received a reward of 300 dollars. We have not been able to find out whether the doctor received any recompense, it is quite likely that, as has been customary for centuries, he rested content with the knowledge that virtue is often its own and only reward. The experiment showed conclusively that without mosquitoes infection is not transmitted, at any rate that the soiled clothing of even fatal cases is not directly infective.

While not wishing or intending in the least degree to detract from the fortitude of these investigators, we ought to mention, if only as a matter of history, that they were not the first to make this terrible experiment (see p 351 and the experiments of Firth in 1793 and the observations of Blair in 1850). In 1883 Hirsch had written

Even the most intimate kinds of contact, such as the healthy and the sick sleeping in one bed, the attendance of physicians and nurses upon the sick, the use of the uncleaned linen, clothes or beds of yellow fever patients, post-mortem examination of their bodies and the like, have in no wise contributed to the spread of the disease. [This referred to observations made in 1803, nearly a century before.] Particular emphasis has been laid in some quarters upon the fact that specially designed experiments to induce infection by the inunction or inoculation into the skin of the vomit of yellow fever patients, and by the wearing of the linen clothes used by the sick and saturated with their perspiration, have always yielded a negative result.

The Commission also erected at Camp Lazear a second building similar to the first, but provided with means of free through ventilation and divided by a wire-screen partition into two rooms, 12 by 14 feet and 8 by 14 feet. Instead of soiled bedding all linen supplied was carefully disinfected. Into the larger room fifteen mosquitoes were liberated which had previously fed on yellow fever patients in the early days of their illness. One of these had bitten twenty-four days before, three twelve days before, the other eleven eight days or less, that is, one was certainly and three others possibly infective. Three non-immune Americans took up their abode in the smaller room, screened from that with the mosquitoes, and one of them, J J Moran, went into the other room and was bitten freely by the liberated insects. In just under four days symptoms made their appearance and the man suffered from an attack of yellow fever, his two companions remaining in good health.

The Commission made a comprehensive series of experiments to test the infectivity of the blood of yellow fever patients. They injected directly from sick to healthy the blood of a patient on the second day of fever. A dose of 2 c c set up an attack after an interval of four days, 1.5 c c abstracted twelve hours after the onset of symptoms and injected into a non-immune resulted in infection, the onset of symptoms occurring after three days, 0.5 c c taken on the second day of fever caused on injection a mild attack after an interval of two days. One c c from this second patient, abstracted twenty-seven and a quarter hours after onset of symptoms, gave rise to an attack in a third subject on the third day subsequent to injection. It was also found that 0.1 c c of serum from blood taken from a patient on the first day of illness gave rise to an attack by subcutaneous injection. The Commission had no doubt that the mild attacks set up were yellow fever, nowadays, of course, the question would be definitely settled by resort to the mouse protection test. These patients were fortunate, for Dr Guiteras carried out similar inoculation experiments in Havana and of seven so inoculated three died and he consequently put an end to his experiments.

It is impossible to eulogize too highly the intrepidity and courage of these volunteers. Three of those who had exposed themselves in the experimental huts to possible infection by fomites—Privates Levi E. Folk, W. G. Jernegan and James L. Hanberry—submitted to mosquito inoculation or injection of infective blood, and all three suffered from an attack, thus proving conclusively that they had not undergone what we should now call an 'infection inapparent,' but were at the time of the inoculation and after the exposure to fomites still non-immunes.

The following tables, issued with an official memorandum of the United States War Department, 30th August, 1906, give all the necessary details. Seven were Spanish immigrants whose risk was equally great but whose courage was tempered by the fact that they were willing to take that risk for a promised pecuniary reward, the others, though some of them were subsequently given a small recompense, offered themselves solely for the cause of humanity and science. Of these one, John J. Moran, was a civilian clerk who refused all recompense, another, John R. Bullard, was a Harvard graduate and a well-known athlete. The remainder, except Drs. Carroll and Cooke, were American soldiers.

TABLE I

No	Exposed to Fomites	Taken Sick
1	Dr R P Cooke	—
2	Levi E Folk	—
3	Warren G Jernegan	—
4	James L Hanberry	—
5	Edward Weatherwalks*	—
6	Thomas M England	—
7	James Hildebrand†	—

* Unaffected by exposure to fomites Later submitted to mosquito bite, but did not contract infection When Hanberry fell sick Weatherwalks refused further mosquito inoculation

† Volunteered for inoculation, but because of his age, he was refused

TABLE II

No	Infected by Mosquitoes	Taken Sick
1	Dr James Carroll	31st August, 1900
2	William H Dean (recorded at first as X Y)	6th September, "
3	John R Kissinger	8th December, "
4	Nicanor Fernandez	13th " "
5	Antonio Benigno	" " "
6	Becente Presedo	15th " "
7	John J Moran	25th " "
8	Jose Martinez	3rd January, 1901
9	Levi E Folk	23rd " "
10	Clyde L West	3rd February, "
11	James L Hanberry	9th " "
12	Charles G Sonntag	10th " "
13	Pablo Ruiz Castillo	19th September, "
14	Jacinto Mendez Alvarez	13th October, "

TABLE III

No	Infected by Injection of Blood	Taken Sick
1	Warren G Jernegan	8th January, 1901
2	William Olson	11th " "
3	Wallace Forbes	24th " "
4	John H Andrus	28th " "
5	Manuel Gutierrez Moran	20th October, "
6	John R Bullard	23rd " "

TABLE IV

No	Infected by Injection of Filtered Blood Serum	Taken Sick
1	P Hamann	19th October, 1901
2	A W Covington	" " "

The conclusions reached by the members of the American Commission in Cuba were as follows

1 The mosquito (*C. fasciatus*) serves as the intermediate host for the parasite of yellow fever

2 Yellow fever is transmitted to the non-immune individual by means of the bite of the mosquito that has previously fed on the blood of those sick with this disease

3 An interval of about twelve days or more after contamination appears to be necessary before the mosquito is capable of conveying the infection

4 The bite of a mosquito at an earlier period after contamination does not appear to confer any immunity against a subsequent attack

5 Yellow fever can also be experimentally produced by the subcutaneous injection of blood taken from the general circulation during the first and second days of this disease

6 An attack of yellow fever produced by the bite of the mosquito confers immunity against the subsequent injection of the blood of an individual suffering from the non-experimental form of this disease

7 The period of incubation in thirteen cases of experimental yellow fever has varied from 41 hours to 5 days and 17 hours

8 Yellow fever is not conveyed by fomites, and hence disinfection of articles of clothing, bedding, or merchandise, supposedly contaminated by contact with those sick with the disease, is unnecessary

9 A house may be said to be infected with yellow fever only when there are present within its walls contaminated mosquitoes capable of conveying the parasite of this disease

10 The spread of yellow fever can be most effectually controlled by measures directed to the destruction of mosquitoes and the protection of the sick against the bites of these insects

11 While the mode of propagation of yellow fever has now been definitely determined, the specific cause of this disease remains to be discovered

At the discussion which followed the enunciation of these conclusions, at the Pan-American Medical Congress held in Havana, 4th-7th February, 1901, it was remarked that the mosquito in question did not belong to the genus *Culex*, but to the *Stegomyia*. Later, as we know, it became known as *Stegomyia fasciata*, then as *Aedes argenteus* and now as *Aedes ægypti*.

By these investigations, these experiments, so beautifully planned and executed, the chief points in the epidemiology of yellow fever were explained and incidentally they brought home to those concerned how vast must have been the loss due to old-time methods of ship-quarantine, jettisoning of cargo, house quarantine, destruction of effects, use of disinfectants, from want of knowledge of yellow fever and its mode of conveyance. Their investigations had cleared up many age-long difficulties and

explained the mode of spread of infection by the breeding of the mosquitoes in water collections, especially domestic, such as cisterns, vases, tubs, tins, etc., the periodicity and seasonal prevalence in areas where there was a cold winter and a hot moist summer, the low temperature of the former checking breeding of the vector, extension of the infection and outbreaks of the disease along trade-routes. The observation was quite an old one that from the moment Europeans settled among native races in the tropics and began to trade, yellow fever appeared. Thus Howard, on his visit to Mexico (in 1904), found the mosquito very abundant from the city of Mexico to Vera Cruz. At Orizaba they were less and had been seen there only in recent years. They had been brought by the railway and had gradually spread into the city and were found breeding in domestic water receptacles.

It had also long been observed that ships were liable to transmit the disease from one part of the world to another, or transfer it by means of lighters working a ship near shore. Shipboard yellow fever might arise in two ways: either from a seaman coming on board in the incubation period of his illness while uninfected mosquitoes were harbouring in the ship, in the hold, for example, and later becoming infected when the man's illness developed, or from infected mosquitoes gaining access to the ship and biting the men. In the former case an interval of at least a fortnight would elapse between the first and the second case, in the latter the sequence might be rapid, cases occurring even simultaneously. A very great danger, as is well known—but the knowledge is the outcome of the Commission's researches—is the early case, particularly the overlooked or (it is sad to have to say it) the wilfully ignored case, for it is in the first days that man is most infective and if *Aedes* bite him each may become a focus for further spread of the virus.

All this was even more firmly established when the habits and life-history of the vector became more clearly known. These insects were shown to be particular as to the places for oviposition, many mosquitoes will oviposit in any marsh, mud-puddle, dirty brook, hoof-mark water, and so forth, *Aedes* prefers and often is found almost limited to the proximity of houses and breeds in cleaner water, often in artificial containers—pans, flower-pots, tins, utensils, anti-formicas (receptacles containing water in which stand the feet of meat-safes, beds, flower-bowls and such like, to prevent the ravages of ants). One of the synonyms of *Aedes* is the 'cistern' mosquito, and only when debarred from fresh-water receptacles will it oviposit in gutters, pools and wells. If found

in a house it may be inferred that the breeding-place is near at hand, and though larvæ soon die if deprived of water the eggs may persist and retain vitality for a long time in an emptied barrel. They have been found viable after twenty days' drying and even after freezing. During the cold weather these mosquitoes remain indoors in a more or less quiescent state, resuming activity on the return of the warm weather and are still infective since, so far as is known, once infected they retain their infectivity for life. Hence in the history of epidemics, in the United States, for example New Orleans, we note cessation of outbreaks in the cold season, December to May, and lighting up again later, though no fresh introduction can be traced.

To sum up briefly, we may say that *Aedes* is fundamentally a domestic mosquito, it is, in the Western Hemisphere, common in the coast towns (for more detailed geographical distribution see below) along the Mexican Gulf, the Caribbean and Atlantic coast of the tropics and subtropics—"a mosquito of seaports," it has been called. It is, however, by no means limited to seaports, but will follow trade routes inland and in Mexico has been found at an altitude above 4000 feet. Transportation by railways was shown in Guatemala and Spanish Honduras in 1905, by the Puerto Barrios and Puerto Cortez railroads. The belief used to be held that it was a night-biter, it is true it is at its worst between about 5 p.m. and 2 a.m. (see the note on the Baltimore epidemic of 1819, p. 338), but it will attack at any time of day or night. Young mosquitoes have been observed to bite twenty-four hours after fecundation and to bite freely in the daytime, in three or four days they become more nocturnal in their habits¹ but if fasting or in captivity they will bite at any time. They lay eggs only after a blood meal, the average periods of development being, at 27° C., between blood meal and laying of eggs three to four days, from ovum to larva the same, larva to pupa seven to nine days, and pupa to imago three to four days, that is 16-21 days altogether.

The geographical distribution of *Aedes* is very wide and the knowledge of this will make us forearmed, because forewarned, against the introduction of infection into countries where yellow fever has not yet appeared, but which may possibly become infected in these days of rapid transport and aviation. It is found in

Africa West and East, in Mashonaland and in Zanzibar, Mauritius, the Seychelles, and in South Africa, the Transvaal

¹ Otto and Neumann deny this, see *Zeitschr. f. Hyg. und Infektionskr.*, 1905

America Lower California, in the Southern United States and along the Atlantic Coast of North America

South Brazil, the Guianas, Chile, Ecuador and Peru

Central British Honduras, Costa Rica, Guatemala, Mexico, Nicaragua, Panama

West Indies All the West Indian Islands and the Bahamas

Asia and the East Indies Arabia, Assam, Burma, the Celebes, Cochin China, India, Japan, Java, Malaya, New Guinea, Palestine, the Philippines, Siam

Australia and Oceania Fiji, the Hawaiian Islands, New South Wales, Queensland, Samoa, the Solomon Islands, South Australia, Victoria

Europe Cyprus, Gibraltar, Greece, Italy, Malta, Spain and Portugal

In short, generally distributed between 40° N and 40° S latitudes

5 APPLICATIONS OF THE FINDINGS OF THE AMERICAN COMMISSION

Dr Liceaga, President of the Board of Health, Nicaragua, a most enlightened man, handicapped by his official superiors, was among the first to accept the conclusions of the United States Yellow Fever Commission regarding the *Aedes ægypti* (*S. fasciata*) as the sole vector. He drew up a scheme for its control and arranged for eighteen inspectors to safeguard different points in the zone under his medical care. The plan was sound in conception but not in execution. Dr Liceaga was unable to obtain eighteen inspectors, after considerable difficulty he found one, an Indian, whose medical and official equipment consisted of a quart tin of kerosene and a badge of authority on his sombrero. Dr Liceaga, though a personal friend of the President, Porfirio Diaz, stated quite frankly that he dare not leave his official headquarters in town to make an inspection of outlying districts because, on his return, he might, and almost certainly would, find that someone else had been appointed in his place.

The clinical facts of yellow fever were so well known and the epidemiological features so determined by the Commission that, although the ultimate cause had not been isolated, nevertheless successful prophylaxis was possible. The work of Reed, Carroll, Lazear and Agramonte was confirmed and followed up by Walter Myers—who, like Lazear, fell a victim—and Durham at Para (1900), by Marchoux, Salimbeni and Simond at Rio (1901), by Rosenau,

Beyer, Parker, Pothin and Francis at Vera Cruz (1903), by Thomas and Breinl at Para (1905), by Guiteras in Havana, and by Lutz, Ribas, Barreto de Barras and Rodriguez in Brazil

We will next proceed to relate an instance or two of the application of the knowledge acquired from the investigations and experiments of the American Commission and the results thereof For this a few words will be said on the Havana, the Rio Santos and New Orleans campaigns, and the Panama Canal Zone

1 *The Havana Campaign*

In the last quarter of the nineteenth century the general condition of Havana from the sanitary aspect was deplorable The streets were narrow and congested and on either side was a fetid gutter, the road was paved unevenly with stones, footpaths were raised but only some ten inches wide and in wet weather or when water refuse was discharged down the streets they became full of puddles, while the harbour was nothing less than a *cloaca maxima* The place was regarded as a trader's paradise The merchants sold imported goods at a high price because duty on them was heavy, at the same time fraud and smuggling prevailed to an enormous extent, so the trader could buy cheaply The introduction of paper money made the vendor less confiding and the prices of commodities which he purchased might in consequence be raised some 50 per cent and he, at no time too scrupulous, promptly doubled his selling prices

The insanitary conditions above mentioned were inseparable from collections of water, largely domestic, which afforded ideal conditions for breeding of *Aedes* and the virus of yellow fever was endemic there and the death-rate from this disease was sometimes very high, though it varied from year to year, probably with the advent or absence of non-immunes In the last five years of the nineteenth century, 1896-1900, the deaths from yellow fever numbered 1282, 858, 136, 103 and 310 respectively In the second half of the century 35,952 deaths occurred from this cause, an average of two a day Between 1905 and 1909 there were only 359 deaths from it throughout Cuba and only 40 in Havana itself, in the opening years of the present century the figures were 310 in 1900 and in the four following years 18, 0, 0, 0, respectively In 1907 only one fatal case of yellow fever occurred in Havana and in April 1909 a Bulletin was issued saying that Cuba was free from smallpox, yellow fever and bubonic plague How had this been accomplished?

William Crawford Gorgas, an officer in the Medical Department of the United States Army, was chosen to take charge of the undertaking (see Life of Gorgas, Chapter XXIII, p. 1039) at a time prior to the researches of the Commission. When he started work in Havana in 1898 the yellow fever situation was certainly less serious than in the years preceding (see mortality, above) and deaths were few, 136, whereas two years before they numbered 1282. The reason for this was that the Spanish Army had returned to Spain and the population was preponderantly native, that is, non-immune susceptibles were relatively few. From the hygienic aspect, however, Havana was little better than a cesspool, deaths from dysentery and typhoid fever were many. Gorgas shared at this time the current view that yellow fever was a 'filth disease' and would be reduced, even eradicated, by cleaning up the city. He carried out vigorous measures, not overlooking a single building, hotels, cafés, stores, bakeries, butcher-shops, private houses, all were attended to, new drainage was installed, refuse disposed of, stable floors cemented, and Havana became a clean town. Intestinal diseases almost disappeared, but to Gorgas's surprise and disappointment yellow fever began to increase. On the cessation of the Cuban War in 1899 a tide of immigration set in and during the following year there were 25,000 new arrivals, mostly non-immune Spaniards from the mother country.

Soon after this the American Commission issued its report and the findings incriminating the *S. fasciata* (*Aedes ægypti*) put the question in a different light and accounted for the non-success of Gorgas's measures of general sanitation in eradicating yellow fever. At first it was not generally known, or, if known, was not a point on which stress was laid, that *Stegomyia* differed from other mosquitoes in its habits, but later it was proved that, owing to its fastidiousness as regards sites for oviposition, this mosquito was less difficult to deal with than either *Anopheles* or *Culex*. Gorgas reviewed his previous work and had records made of every house and every possible container. What this must have entailed, what wonderful tact in dealing with an excitable and easily provoked Latin race only those who know something of the latter and have had the privilege of knowing Gorgas personally are capable of gauging.

We need not go into the question in further detail, suffice it to say that whereas for nearly a century and a half, from 1762 to 1901, there had not been a day when yellow fever was not present in Havana, and in the decade preceding the American occupation had taken a toll of some 500 lives annually, from

March 1901, when Gorgas undertook the special anti-*Stegomyia* campaign, there were only five deaths, in the ensuing July and August. In 1905 there were the beginnings of another outbreak, which, however, was promptly checked by application of Gorgas's methods, and since then there has been no further outbreak.

The main principles of his methods are enunciated by Gorgas himself in the *Journal of the American Medical Association*, in 1909

1 Promulgation of an ordinance declaring it a nuisance for any owner of property to have mosquito larvæ on his premises. Anyone convicted to be fined.

2 Establishing an ordinance giving a sanitary officer authority to abate these nuisances if, after receiving a week's notice, the owner does not attend to the demand, the costs for this intervention to be recoverable through the courts.

3 Abolition or screening of any collections of water likely to breed mosquitoes [especially domestic collections and *Aedes*].

4 Division of the municipality concerned into districts, each in sanitary charge of an inspector. Usually twenty-five houses can be inspected daily. A report had to be furnished monthly on each house and a daily report of the houses seen and the action taken when deemed necessary.

5 Every suspected case to be reported to the Health Officer and the patient screened at his house or in hospital.

II *The Campaign in Rio and Santos, in 1903*

Outbreaks, many of them of a devastating character, followed the introduction of infection in the seventeenth century, probably, it was believed, from the Antilles. In the last decade of the nineteenth century when Brazil was expanding and many young men—clerks and artisans—were immigrating thither, the morbidity and mortality rates among such non-immunes were naturally high. It was estimated that nearly 60,000 [the figure is given as 58,335, but this cannot be so accurately stated] lives were lost from yellow fever in the second half of the century. As regards individual years in 1891 deaths from the disease numbered 4456, in 1894 and 1898 the numbers were 4312 and 4852 respectively.

Oswaldo Cruz started a hygienic institute in Rio, bringing together an able body of assistants, and, with the hearty support of the Government, succeeded speedily in getting rid of yellow fever. In 1902 there were 984 deaths recorded from this disease in Rio de Janeiro, in 1909 there was none, and this happy result is ascribed to active anti-mosquito measures directed particularly against *Aedes ægypti*, in spite of the fact that from 1903 onwards, and for the next three years particularly, there were more immi-

grants than in the years preceding Santos, once known as 'Le tombeau des étrangers,' was transformed into a true 'Santos'—a blessed place, a health resort

In spite of a demonstration, apparently so striking, and of the work of Reed and Carroll, Sanarelli writing in 1906 (*Rev d'Hygiène et de Police sanitaire*) still maintained that his *B icteroïdes* was the cause of yellow fever and expressed disbelief in the mosquito views Santos, he states, became free from yellow fever the same year as Havana, although no mosquito destruction was carried out in the former [this is difficult to understand in consideration of the efforts of the Oswaldo Cruz Institute staff], and therefore there are no real grounds for ascribing the disappearance of yellow fever in Havana to the vigorous anti-mosquito campaign

III *The New Orleans Campaign, 1905*

The population of New Orleans at this time was estimated at 325,000, and among them many Italian and Sicilian labourers living in the oldest and dirtiest part of the town Yellow fever seems to have gained a considerable hold before it was recognized Then appeal was made to the municipal authorities and others with influence for application of sanitary measures, and to the medical men for dealing with the clinical side The former included

- (i) Appeal to the people to empty their domestic water receptacles, and to oil their cisterns or to screen them
- (ii) To the people to sleep under mosquito-nets
- (iii) Appeal for Civic co-operation to support these suggestions
- (iv) Appeal to the medical men (see below)
- (v) Appeal to the clergy and others who had the opportunity to announce to the people information regarding yellow fever and its mode of contraction

As the result of the above a water-cistern screening ordinance was promulgated, a day was appointed for a 'thorough clean up' of the city and a request was made to the householders to observe a 'general fumigation day'

The medical men who were not experienced in the clinical course of yellow fever were to be notified that black vomit does not occur in the majority of cases and, therefore, they ought to report to the health authorities all cases of fever seen by them in the epidemic zone, so that mild cases might not be missed and that precautions might be taken in the early stages, that the Board of Health should be authorized to appoint a commission of experts

who should see all such cases and on them should rest the responsibility of diagnosis, that all cases of yellow fever and all those suspicious should be promptly removed to hospital and protected by screening and nets, though in exceptional cases those who were under suspicion only might be treated in their homes, if the rooms were protected by wire screens and the patients were under mosquito-netting

The results may be stated quite briefly. The epidemic broke out in July, by 12th August 105 cases were occurring daily. By careful attention to early cases, by removing patients to screened hospitals and thus isolating the sick, by eliminating domestic mosquitoes, results were becoming apparent in three weeks from the first notifications. The sick were removed from the healthy, no fresh broods of *Aedes* were being hatched, because they had no access to water, and infected mosquitoes were being killed. No attempt was made at special disinfection of fomites, fouled linen and effects, these were washed in the ordinary way with other articles at the laundry.

IV *The Panama Canal Zone, 1904*

Details of the medical difficulties encountered in the construction of the Panama Canal and how they were overcome are given elsewhere (see *Life of Gorgas and the Panama Canal*). Here the merest sketch must suffice. The project seemed so simple, a mere forty miles separated the Atlantic from the Pacific, but the forty miles were 'one sweltering miasma'—an apparently hopeless tangle of tropical vegetation, swamps of ungauged depths, black muddy soil, quicksands, intercepted by a volcanic mountain or a river which at certain seasons might rise twenty feet in a night. Anthony Froude writes of it in 1885

In all the world there is not perhaps now concentrated in any single spot so much foul disease, such a hideous dung-heap of physical and moral abomination. The Isthmus is a damp, tropical jungle, intensely hot, swarming with mosquitoes, snakes, alligators, scorpions and centipedes, the home, even as Nature made it, of yellow fever, typhus and dysentery,

and, he might have added, malaria.

Gorgas, on the strength of his reputation and wonderful success in Havana, was the obvious man to be put in charge of the medical side in Panama. When in March 1904 he made a preliminary inspection he found no signs of yellow fever, because, although the disease was endemic there, there were practically no strangers in the Canal Zone. Three months later he arrived with a small band

of zealous devotees—J L le Prince, Dr Carter, Dr J Ross, Dr Louis Balch, Dr Louis A la Garde, Major J Turtle and Miss Hibbard, the head nurse, but without even the most necessary supplies—no official backing, no sanitary force, and short of funds. The local authorities were not going “to spend good American dollars on a group of insane enthusiasts who spent their time chasing mosquitoes,” for they, “as everyone, knew that what caused yellow fever was not mosquitoes, but filth and dirt.” In November, with many susceptibles, non-immune arrivals—engineers, officials, labourers—came Nemesis and an epidemic was soon under way. All who could wanted to clear off for home and the fate of the vast project, an undertaking which had ruined de Lesseps, might be said with justice to rest in the hands of one man, Gorgas, with the support of his small band of enthusiasts.

Gorgas took the matter in full earnest, he saw to it that domestic water receptacles—the water-supply of Panama and Colon was the rainfall—must be eliminated or protected from access by mosquitoes. He instituted an ‘*Anopheles* brigade’ to deal with malaria mosquitoes, and a ‘*Stegomyia* brigade’ for the vector of yellow fever. A law was passed making penal the harbouring of mosquito larvæ on private premises, the city, as in the case of Havana, was divided into districts each supervised by an inspector. The mosquitoes, deprived of domestic receptacles of water for oviposition, found sufficient water in the large-leaved vegetation, in crevices of wayside stones, in thrown-out tins, in the holy-water stoups. It was impossible to deal with all these in a brief period, so advantage was taken of the habits of *Aedes* in preferring clean water to set out basins of it in selected spots. Finding as they probably thought (if a mosquito thinks) that their former haunts had been swept and garnished, they laid eggs in millions. The basins were emptied, the eggs destroyed and fresh water placed ready. This, aided by removal of pans, of water-jars, barrels, refuse tins and so forth proved very effectual. At the same time patients were removed to isolation, mosquito-nets put into general use, and in six months a scourge which had ravaged the district for four centuries had been practically eradicated.

The vexatious controversies, the numerous pin-pricks, obstruction on the part of officials who knew no better, though they ought not, after the experience of Havana, to be excused altogether on the plea of ignorance, all this is referred to in the account of the Life of Gorgas (see p 1034).

To sum up, the report of 1908 stated that as the result of the measures enforced,

It is now more than three years since a case of yellow fever has developed in the Isthmus, the last occurring in November 1905. The health and sick rates will compare favourably with most parts of the United States.

The opening of the Panama Canal, though of inestimable benefit commercially and a lasting record of the triumph of engineering skill, rendered possible by the sound application of medical knowledge, caused no little searching of heart as to the risks of the spread of yellow fever from the West to the East—to India, Australia, China, Japan. Most of India's sea-borne trade was with Europe and introduction of the infection was not a serious menace, for the distance between London and India by the new route *via* Panama was fully 10,000 miles longer than that *via* Suez. A similar argument applies to the likelihood of transmission from the United States to India, since New York was 6800 miles nearer by the Suez route and New Orleans less than half this, 3200, as compared with that by way of Panama. As regards the endemic areas—the West Indies, Mexico, Central American Republics, the Panama Canal Zone, Colombia, the Guianas and Venezuela—the older route *via* Suez was still the shortest, and from Brazil *via* the Cape. If trade increased between India and the Pacific coast ports of South America, Peru and Chile, the best route again would not be across the Pacific but from Callao and Valparaiso *via* the Straits of Magellan and the Cape.

Ports farther east were certainly subject to a greater menace for the voyage to the Far East—China, Japan, the East Indies and Australia—would be considerably shorter by way of the new canal. Hong Kong was thus in almost direct communication and also certain ports of Japan, Nagasaki, Kobe and others, whence infection, if introduced, might be conveyed farther to Australia and the East Indies on the one hand, and the Straits Settlements on the other.

At the same time we must remember that it is from Vancouver and San Francisco, neither of them yellow fever centres, that traffic passes from the West to the East. The menace, however, such as it was, has been much reduced since the beginning of the present century by the practical eradication of the infection from Rio de Janeiro, Cuba, Colon, Panama and New Orleans.

The Hawaiian Islands are in a less safe position because vessels from America to the East often make them their first port of call, precautions, however, are taken and thoroughly enforced, and the

northern route to Hong Kong from Honolulu traverses latitudes which are not favourable to the vector. Ships from San Francisco to the Philippines, calling at Honolulu *en route*, do not touch Japan, so that Japan is unthreatened while Honolulu and the Philippines are free.

Oceania, we have seen, is within the geographical distribution of *Aedes*, and infected mosquitoes could remain alive in transit and possibly find a chance of breeding, so that Australia, for example, is not exempt. On the modern, well-ventilated ships the likelihood of survival of infection in *Aedes* is small. In 1915, a Quarantine Service Publication (No. 6) of the Commonwealth of Australia gave an excellent summary of facts bearing on the question of the opening of the Panama Canal as regards the possible introduction of yellow fever into the country. In this the geographical distribution of yellow fever is given, and a map shows places adjacent to Australia where *Aedes* has been found. A later section records the results of a survey of the chief coastal towns of Queensland, this mosquito was found to be abundant and if yellow fever were introduced the spread of infection might be rapid and wide. The conclusions drawn were that the greatest menace was endemic foci on the Pacific Coast of America, but that the opening of the Canal would bring other foci in their range and more particularly might danger arise from ports *en route* to Australia becoming infected and so acting as 'relay stations'. Since the northern ports of the eastern coast harbour *Aedes* in numbers and early cases constitute the grave danger, the report contains a clinical description so that quarantine officers may be on their guard. Trade between America and Australia was steadily increasing and therefore it was essential to take steps to reduce the *Aedes* prevalence in the Australian ports, as had been done in Panama. Otherwise, if infection were introduced, the loss of life would be heavy and the dislocation of commerce and detriment to shipping very serious, hence the advisability of supporting James's proposal of an intelligence officer, trained in sanitary administration, stationed at Panama to act as an outpost for Australasia, and it would be well also to have such an officer in Samoa or Tahiti, if vessels from America make these places regular ports of call. The most important question, from the Australian view, is reduction of the local mosquito prevalence, in particular, of course, *Aedes*.

Though countries where yellow fever has never been known might be taken unawares, there is little or no excuse for allowing

conditions fostering the spread of mosquito-transmitted infection to persist in centres known to be endemic. Ignorance cannot be pleaded in extenuation there. As recently as 1935 cases occurred in the Gambia and a sanitary survey was undertaken—verily, a closing of the stable door after escape of the steed. This revealed innumerable potential breeding-places for *Aedes*—thousands of tubs, barrels, oil-drums, kerosene tins, calabashes, discarded food-tins, bottles, old buckets, basins, open water-tanks and so on in some 3000 compounds, wells, over seventy in number, quite unproofed, eaves and gutters were found to be harbouring larvæ in spite of two months' dry weather, lighters and canoes on the foreshore held small collections of water, as did also many of the crab-holes. More than a quarter of a century before, in 1908, an African inspector had written "I find from experience the greater part of the mosquitoes come from the cotton trees," nevertheless the survey reported finding hundreds of flamboyant cotton- and baobab-trees with cavities holding water, some even gallons of it, and actively breeding mosquitoes. Smaller collections almost equally dangerous could not be eradicated without cutting down the trees, for the dews are heavy and condense on the bark and the water runs down, replacing what may have been lost by evaporation. Nearer the dwellings, soakage pits, both those for the standpipes and for the water running from baths and sinks, were found in most cases full to the top with water, and the earth ditches at the road-sides were badly graded, overgrown with grass and containing stagnant water.

It is but a truism to say how easy it is, once the immediate danger is over, to return to the thoughtless neglect which was the direct cause of a late catastrophe and it is an ever-recurring difficulty for public health measures to retain in a Government programme the prominent place their importance merits.

We trust it will not be considered a waste of time if we gather up the loose threads of this section dealing with the epidemiology of mosquito-borne yellow fever and epitomize this aspect of the subject as it has developed since the investigations of Reed, Carroll and the other members of the Commission at the beginning of the present century. For the past twenty years the details can be studied in the many enlightening reports of the *Yellow Fever Service of the International Health Division of the Rockefeller Foundation*.

The twenty-five years following the demonstration of the proof that *Aedes* was the vector of the virus have been spoken of, most

aptly, by Dr F L Soper, as the Golden Age of achievement in eradication of yellow fever, first in the 'key centres' such as Havana and Panama, and by this means in the West Indies, the Caribbean and the Mexican Gulf which have been constantly fed, as it were, from the key centres. Similarly, Southern Brazil was freed by the campaigns in Rio and Santos. In 1915 the Rockefeller Foundation International Health Board took control with its accustomed energy, vigour and thoroughness, and in the succeeding decade yellow fever died down on all fronts. Then followed another decade which Dr Soper calls the Age of Disillusion, when, in spite of all anti-Aedes methods, the infection remained. We shall deal later with jungle yellow fever, or yellow fever in the complete absence of *Aedes ægypti*.

By 1919 Guayaquil, Ecuador, on the Pacific Coast, and a small area in north-east Brazil down to Salvador, Bahia, were believed to be the only foci remaining of any importance in South America, and anti-mosquito measures eradicated it from Guayaquil. In the second, Brazil, efforts were less successful and, candidly, failed, being practically discontinued in 1920. Three years later the Rockefeller Foundation was asked to take the matter in hand, they complied and in two years it was thought that the problem had been solved, the enemy overcome. But, the following year, 1926, an outbreak occurred in the interior of north-east Brazil, due, it was believed, to the movement of non-immune troops and the "lighting up and fanning to a visible flame the dying embers of infection which otherwise would have spontaneously disappeared" (Soper). For, as H R Carter had explained ten years before when discussing the question of spontaneous disappearance of the disease from failure of the human host, since an attack confers permanent immunity, in course of time no susceptible people will remain and when the infected mosquitoes die off, only a fresh introduction of the virus can start an outbreak. He is inclined to think that this theory explains its disappearance from many places, but this assumes that there are no births and no immigrants. It was the immigration of susceptible soldiers that, as we have just seen, resulted in the fresh outbreak in north-east Brazil. More vigorous application of anti-mosquito measures was rewarded by apparent success and for almost a year no case was seen. Then, in 1928, more cases appeared in Rio de Janeiro and continued to do so till July 1929, with locally infected persons in the neighbouring states of São Paulo, Minas Geraes, Sergipe, Pernambuco and Para and up to Manaus, an inland port on the Amazon. Cessation of the Rio outbreak led to the disappearance of these

outlying infections The same year, 1929, outbreaks of unknown origin occurred in Colombia and Venezuela.

The following year, 1930, the viscerotome was introduced and in 1931 the mouse-protection test, these opened up a new era in the epidemiology of the disease, and are considered later in the section dealing with recent work (p 411 *et seq*)

6 THE CAUSE

The final conclusion of the American Yellow Fever Commission in Cuba, 1901, was "While the mode of propagation of yellow fever has now been definitely determined, the specific 'cause' of this disease remains to be discovered" We will now take up the question of the ætiological agent, in its historical aspect

Early ideas, in this as in other infective diseases, were, as regards causation, of a vague character Seeing that outbreaks usually started or were severest in the coastal towns, in the neighbourhood of harbours and wharves, in the dirtiest quarters of these towns, in the narrow and foul streets and congested, overcrowded tenement dwellings, or in ships with small dirty holds, people naturally ascribed the disease to the general dirt and filth Next, from the tendency to confuse yellow fever with malaria in some of its forms, the idea that it arose from soil and damp began to gain adherents, while the fact of its prevailing at times on board ship was held as proof that, though damp might play a part, the spread of infection at least was quite independent of soil influence Further, there were difficulties in explaining ship outbreaks, even on the moisture theory, because it had been noted how on board ship those on one side, even one deck, might be attacked at a considerable interval before the rest of the vessel was invaded and that not uncommonly the sailors might suffer while the officers escaped It was held that two main factors were necessary for extension, namely, a miasma and an atmosphere infected by aggregation of the sick Mere high temperature alone could not bring it about, moisture was essential and "a rapid decomposition and exhalation of organic remains" resulting therefrom But even at altitudes usually dry the conditions after heat and rain might furnish "by chemical decomposition of the soil, the specific miasm of yellow fever" The foul state of the holds on board were thought to provide a similar combination of causal factors

There were, however, arguments brought forward which were difficult to reconcile with these opinions, general and vague though they were Thus, Fergusson in 1843 noted that—

In the West Indies are regions free from swamp . Send European troops there and, provided the place be on the coast, they will be decimated by yellow fever as surely as if we had sent them to Demerara or to any other of the most swampy places in the world

Again, on the other hand,

The yellow fever of Charleston has never extended to the swampy districts of South Carolina, nor from Mobile over the damp flats of Alabama and, whereas malarial fevers have decreased remarkably in Charleston within recent years in consequence of improved drainage, yellow fever has continued as frequent and as malignant as before

We have noted already when speaking of the general notions regarding the disease, how it was thought that in the Western Hemisphere certain poison germs—among them that of yellow fever—arose spontaneously in most, if not all, of the West India Islands and that they might retain their virulence for an unknown length of time in the holds of ships, in storehouses, and in personal effects, and in decaying animal and vegetable matter or soil containing such

Hypotheses as to the nature of the poison have varied with the ingenuity of their proposers Audouard, in 1824, maintained that it was engendered in the crowded, filthy, unventilated holds of slave ships and that it was by their means that the West Indies and America first became infected In 1858 Lawson remarked that

Healthy persons going into a locality where the cause [of the disease] was known to be in a state of activity were very liable to be attacked, but if they or others infected in such a locality returned to a healthy one, they went through the fever there without communicating it, there was no evidence to show that persons labouring under the yellow fever, or the bodies of those who died of it, gave off a poison capable of exciting the disease

Nevertheless, epidemiological evidence pointed to some kind of communicability, because outbreaks followed soon after the arrival of ships from ports where the disease was known to be prevailing at the time of their departure In most cases, it is true, there were cases of yellow fever on board when the ship arrived, or there was a history of its having attacked members of the crew on the voyage, but instances were met with in which there was no history of any case on board, and the vessel seemed to bring infection—a state of things very puzzling at the time, but quite clear now with our knowledge of mosquito transmission

Guyon noted in connection with the Lisbon epidemic of 1857 that

Once in a house the scourge will always carry off a larger or smaller number of victims from it, further, *whether there are still sick persons in it, or whether there are no longer any, that house will become a centre to reproduce the disease in the strangers who enter it*

Macdonald, who was an ardent partisan of the parasitic theory, was very scathing in his contempt of those who maintained that the disease could arise spontaneously

There is no more proof [he says] of the spontaneous development of a monad than of an elephant, the doctrine of the spontaneous origin of the yellow fever organism or cause can have no foundation to satisfy the rational mind

In the *Lancet* of 1869 (II, p 583) is a report from Bermuda giving an instance of what was regarded as the clinging of the morbid poison of yellow fever to rooms

The naval authorities told off a number of sailors to clean out the quarantine hospital, and the work had just begun when a ship arrived from the West Indies with yellow fever on board. As the sick from this vessel had to be taken into the hospital, the cleaning was put off for a time, and the sailors ordered back. Twenty-seven days after the last convalescent had left the hospital to go on board and the vessel had sailed again for Halifax, the sailors, eight in number, resumed the work of cleaning and within the next eight days two of them sickened and died, a third fell ill six days later, the remaining five were then sent to Halifax on board a sloop-of-war under the charge of a surgeon, who himself took the fever and died

Another writes in 1892

This semi-malarious disease arises like cholera from dirty, damp soil, ships, etc, to which the germ had at some previous time been brought. The places where it is acclimatized are not very many, and it is sensitive to cold, so that with proper cleansing measures, quarantine, and prevention of crowding, it could be rapidly reduced

Importation by ships was explained by Dr William Bailey, Professor of Medicine at Louisville, Kentucky, as recently as 1879 in the following words (*Lancet*, 6th September, 1879) "The transmission rests with the vessel, not with the persons carried by it" What was transmitted was "a section of the climate of a yellow fever district", the ship brought something from the climate and not from the sick. Blankets and clothes of absorbent texture are permeable by the atmosphere of these tainted localities and, when removed,

may long retain some of its peculiar characters. That an atmosphere in which these articles have been kept can thoroughly impregnate them with its own peculiar characters is proved by the odour that so persistently clings to them. I can well conceive, therefore, that when certain conditions—probably combined atmospheric and

telluric—necessary for the production of yellow fever have arisen in a given locality, if they exist in a sufficiently potent and concentrated form, bedding and clothes therefrom may convey in "a section of the climate" the specific contagium of yellow fever, whatever it may be. If this specific contagium, thus derived from the climate of a yellow fever district, is conveyed to a place hitherto exempt, it is allowable to conjecture that under certain favourable conditions it may multiply and thus give rise to another centre, from which the disease may be propagated by similar means (Izett Anderson)

Anderson is not very consistent. He sums up the position in the foregoing words, though previously in the same work (*Yellow Fever in the West Indies*, 1898) he shows that the clothes, bedding and effects of patients ill and even dead of yellow fever are not infective.

Benjamin Rush (1745–1813) was of the opinion that yellow fever was caused by damaged coffee left lying on the wharves and, as we have seen, Dr Sternberg thought that Fort Barrancas had become infected by a barrel of potatoes brought from New Orleans. These are both examples of what is all too common even at the present day of explaining two fortuitous concomitant circumstances as aetiologically related. After all Rush's hypothesis was no more fantastic than the far more widespread belief in malaria being caused by the miasm arising from decaying vegetation in swamps.

As in the case of malaria so in that of yellow fever the causative agent was for a time believed to be bacillary. The first claimant was Sternberg's *Bacillus X*, in 1888, which we need only mention in passing as the claim for its being causative was early abandoned. Sanarelli's *Bacillus icteroides* held the field for a little longer. This was isolated by Sanarelli in 1897 and in the following year he reported (in *Annales de l'Institut Pasteur*) that in Montevideo he had obtained a serum after inoculating horses with the organism and had used it in eight cases of yellow fever, five of them in a critical condition on the fourth day of illness. One of these five recovered after he had been given 80 c c of the serum, and all the other three patients recovered, and two children recovered even though the black vomit had appeared. After each injection a fall in temperature had been observed. To fourteen other patients he gave intravenous injections of serum and "of all so far inoculated 66 per cent have recovered" [presumably nine out of fourteen, in some epidemics the fatality rate is very high, but the average among the unacclimatized is 25–30 per cent. Sanarelli's records above would work out at 34 per cent]. We have seen above (p 354) the claims of this organism were thoroughly exam-

med by the American Commission in Cuba and found wanting—the organism proving to be a close relation of the *Bacterium cholerae suis*

Next in chronological order come certain coliform organisms whose claim to be causative rests on an account by C B Fitzpatrick (1898) who inoculated various culture media with the blood of persons dead of yellow fever. By this means were obtained cultures of organisms named *Bacillus coli concentricus*, the *Bacillus coli ictteroides* and Sanarelli's *Bacillus ictteroides*. A combination of the fluids from these was prepared and employed prophylactically in animal experiments, but nothing has been found in the literature regarding its use in human cases of the disease. Reference has been made to Dr Freire's claim that after inoculating 10,524 persons with "attenuated yellow fever microbes" [they are not specified further] he had reduced the mortality from this disease by nine-tenths.

In 1900, H G Durham and Walter Myers of the Liverpool School of Tropical Medicine reported finding a small bacillus in all the fatal cases examined by them. They stated that it took the usual stains with difficulty and that it grew very slowly when attempts were made to cultivate it, so slowly in fact that "it is possible other observers have overlooked the bacillus"—which was quite true. Their experiments to test its ætiological or other relationship with the disease were cut short by both of them contracting the infection and Myers unfortunately succumbed to it.

John Hunter stated that "fatal yellow fever is the death of the blood" and one cannot be surprised at organisms of some kind or another being isolated from bodies post mortem.

To save having to return again to the supposed bacillary origin of yellow fever we may anticipate the chronological order and refer here to the announcement made by Kuczinski and Hohenadel in 1929, in the *Lancet*, that a coccoid organism isolated and named by them *Bacillus hepatodystrophicans* was the causative organism of the disease. We need say no more than that when weighed in the balances it too was found wanting and has gone to join the organisms of Sternberg, Sanarelli, Durham and Myers.

In 1903 some American observers when examining specimens of *Aedes ægypti* found some protozoa in the diverticula and naturally thought that these might play a part in the causation of the disease. Further investigation, however, proved that this was a frequent contamination and might be found in the mosquito at any time.

Next came Harald Seidelin's *Paraplasma flavigenum*, about which there was no little controversy between 1909 and 1916. In 1909 Dr Seidelin published a paper in *Berlin Klin Woch*, in 1911 another in the *Journal of Pathology and Bacteriology*, and in the following year two more, one in English in the *Yellow Fever Bureau Bulletin* and one in Italian in *Malaria e Malat d Paesi caldi*, on the bodies which he named *Paraplasma flavigenum*. He regarded this as one of the *Babesidae* (the bodies resembled, he said, *Theileria parva*) and the cause of yellow fever. He found them in the red corpuscles, in monocytes and in polymorphonuclear leucocytes. Their appearance is thus described: Small Babesia-like bodies with protoplasm feebly staining blue and a minute chromatin point staining rather a dark violet than the usual red, some (probably older) are larger and show a protoplasm staining a deeper blue and a chromatin point purple when stained. In some of the corpuscles—probably a still more mature stage—there are chromatin granules, single or double, round or pyriform, with or without a narrow border of protoplasm. Seidelin's own opinion of his *Paraplasma flavigenum* was

There can be little doubt as to its protozoic nature, considering its shape and staining reactions, but the forms observed do not suffice to enable us to make an exact diagnosis [of the precise zoological place of the microbe]. The want of pigment and some of the morphological details, such as the double forms and the chromatin bodies almost without protoplasm, would suggest an affinity to the genus *Babesia* (*Piroplasma*) whilst the aspects of the parasite in the kidney would seem to indicate a relation to the Leishman-Donovan bodies (*Herpetomonas*), in other details there is some resemblance to the malarial parasites.

Seidelin sums up by saying

Paraplasma flavigenum was found in practically all cases of yellow fever, in a number of suspicious cases, and in two apparently healthy children, it was not found in other febrile diseases. I, therefore, consider it the pathogenic parasite of yellow fever.

Thereafter many papers appeared, some authors (J E L Johnston, J W Scott Macfie (later Macfie was doubtful and finally against), A Connal) in support of the claim, some (A Agramonte, C M Wenyon, G C Low, D Harvey, Schilling-Torgau, Guteras, David Thomson) against, and some for a time neutral, notably those at first in favour of it.

Coloured plates accompanied the article by Seidelin and that by Johnston and Scott Macfie. In 1914 Drs C M Wenyon and G C Low examined, by the same method of staining, the blood

of healthy guinea-pigs born and bred in London and they found bodies morphologically indistinguishable from Seidelin's *Paraplasma flavigenum*. Their paper also was illustrated in colour and by the same artist as had depicted the figures of Johnston and Macfie's article. Wenyon and Low concluded therefore that

1 In the blood of normal guinea-pigs, born and bred in England, are to be found bodies indistinguishable from the so-called *Paraplasma flavigenum* of Seidelin

2 In most cases these appear to be definite structures which probably have to do with the development or degeneration of the red cells

3 They are not parasitic, because they occur in the blood of newly-born animals, not forgetting even the possibility of a placental transmission [the authors' wording]

4 The apparent success of the inoculation into guinea-pigs of such bodies from yellow fever cases is due to a failure of a sufficient examination of control animals

5 The evidence in favour of the yellow-fever bodies being parasites thus breaks down

6 The presence of such bodies in yellow fever bears, therefore, no diagnostic significance apart from the evidence of blood alteration

The 'blue bodies' described in touch smears of the organs were believed to be identical with Carini bodies found in lung smears made from guinea-pigs and rats

Dr David Thomson also examined the blood of twenty-five guinea-pigs and found the same bodies in twenty-one of them, he concluded that

With regard to the nature and origin of these bodies no dogmatic statement is possible, but that it is highly probable they arise from various sources. Without doubt the great majority of them are artefacts, and cannot be considered as protozoal in nature, though some of those consisting of a reddish ring with a darker staining centre may possibly be an early stage in the *Lymphocytozoon cobayæ* (Kurloff bodies), which were found in practically all of the guinea-pigs examined

The *West African Yellow Fever Commission* considered the question of the occurrence and significance of the 'Seidelin bodies' very carefully, thoroughly and judiciously, and expressed its opinion fully in their Third Report, dated 1st November, 1915. Of this the following is a summary. The authors of the Report—Sir James Kingston Fowler, Sir W. F. Simpson, Sir Ronald Ross, Sir William Boog Leishman and Dr (later Sir) Andrew Balfour—in order to clear the ground begin by stating succinctly the then known facts concerning the virus of yellow fever, also Dr Seidelin's views of these facts and the relationship between Seidelin's bodies and yellow fever

1 It [the yellow-fever virus] is certainly transmitted by the *Stegomyia fasciata* [now *Aedes ægypti*] It is not known to be transmitted under normal conditions in any other way

Dr Seidelin is of opinion that "the axiom that Yellow Fever is transmitted by no other mosquito than the *Stegomyia fasciata*" is "an assertion entirely without proof" and also that "Yellow Fever is transmitted in nature by no other means than mosquitoes has never been proved, but is extremely probable in view of our knowledge of protozoal diseases"

It might have been added "and in view of our knowledge of the effects upon the incidence of the disease afforded by the destruction of the *Stegomyia fasciata*"

2 The transmission can only take place after the Yellow Fever parasite has undergone a development in the mosquito, the duration of which is, approximately, twelve days

Dr Seidelin considers that "this theory is likely to be correct, but has not been conclusively proved"

3 The virus will pass through a Berkefeld filter and belongs to the class to which the term ultramicroscopic is usually applied

It has been objected that the parasite as described by Dr Seidelin cannot be supposed to be able to pass through a Berkefeld filter Dr Seidelin meets this objection by the suggestion that there may be an earlier stage in the evolution of the parasite in which it is invisible and able to pass through the filter

4 The blood of the Yellow Fever patient is infectious only during the early period of the disease, probably not after the third day

Dr Seidelin does not accept the view of "the three days' infectiousness", he believes that "a dogma in medicine has never been established on poorer evidence"

The Board next discuss the propositions which follow and must be admitted if the *Paraplasma flavigenum* is to be accepted as the cause of Yellow Fever

Firstly, they are found in the blood of yellow-fever patients and absent in other conditions, secondly, they are found in the blood and tissues of guinea-pigs, white rats, dogs, and monkeys, after inoculation with the blood of patients, thirdly, it follows that these animals are suffering from the disease, fourthly, the disease may be transmitted to successive generations from such animals by subinoculation and in them the specific bodies are found, lastly, if these bodies are present in the blood or tissues of animals which have not been thus dealt with such animals are the subjects of natural infection

Their investigations led them to conclude, in respect of these propositions

1 That these bodies have been found in many cases of yellow fever

2 That they may be found in the blood of animals inoculated from yellow-fever patients, but it has not been shown that they were absent in animals not so treated, and though the suggestion that uninoculated animals harbouring the parasite were reservoirs of yellow

fever is ingenious, better proof would be the results of scientific research for them in animals of the same species which had never been in a yellow fever country

3 The statements that pyrexia was produced in the inoculated animals, and albuminuria, with presence of the *Paraplasma* in the peripheral blood during life and in the tissues after death, together with lesions in the kidneys and alimentary tract similar to those found in yellow-fever patients—these assertions, they concluded, were not supported by the evidence

The final conclusions, therefore, of the Commission were

1 That no proof has been given that the bodies named *Paraplasma flavigenum* are of protozoal origin

2 That under that name a number of microscopic objects are included

3 That, excluding artefacts, the origin of most of these objects is at present uncertain, and so far none have been proved to possess any definite physiological or pathological importance

4 That there is so far no reason to regard any of these objects as the cause of Yellow Fever

5 That the nature of the virus of Yellow Fever still remains undetermined

The next three years were busy years of the Great War and the problem of elucidating the causation of yellow fever was left in abeyance. Then, in 1918, the attention of all interested in tropical medicine was drawn to a recent announcement of the discoveries of Hideyo Noguchi in the field of yellow fever research, and the ensuing decade is a time to be noted in the history of the causation of this disease and we must deal with it in some detail.

In the *Journal of the American Medical Association* and in the *Journal of Experimental Medicine*, 1919, Noguchi gave an account of investigations carried out in Guayaquil, Ecuador, and of his experimental work in connection therewith. He injected guinea-pigs with the blood of 'yellow-fever patients' and after an interval a rise of temperature occurred and albuminuria was observed and the urine contained casts. The temperature fell by lysis and other serious symptoms made their appearance—jaundice, hæmorrhages from nose, mouth and bowel, black vomit, anuria and coma. Examination of the blood of these animals revealed an organism resembling the *Leptospira* (or *Spirochæta*) of infective jaundice—*L. icterohæmorrhagiae*—which had itself been discovered by Inada and Ido, Japanese investigators, in 1915, and shown by them to be the cause of a disease described by Weil in 1886 and known, therefore, as Weil's disease, or infectious, or epidemic jaundice. Noguchi found this organism, which he called *Leptospira icteroides*, in the liver and kidneys also of his experimental

animals [It will be seen later that in the outbreak he was studying there were probably, nay there must have been, cases of Weil's disease amongst those of true yellow fever and that the train of events was started by his taking the blood of one of these patients for his animal inoculations. He pleaded in excuse, later, that he took the word of a local practitioner that the specimen was from a yellow-fever patient—a strange lapse for a man with a scientific training and acuteness of intellect—but we are anticipating.] With this organism he carried out Pfeiffer's reaction and obtained positive results. Further, he claimed that the blood of infected animals after filtration through Berkefeld V and N would reproduce the disease when inoculated into other animals. [The leptospira may be at some stage, possibly a granule stage, filtrable.] Also that "some of the guinea-pigs were protected from fatal infection by the serum of convalescent yellow-fever patients" [For this to be true there must have been a second error of diagnosis, and the protective serum would be that of convalescent infectious jaundice patients.] This, now but a surmise, would seem to gain support from the fact that eight only out of seventy-four guinea-pigs inoculated with the blood of patients showed signs of disease, but, he stated, *all* were found to be immune to injections of his *Leptospira icteroides*. His thesis was strengthened by his finding that the serum of convalescents from yellow fever agglutinated the organism and also protected guinea-pigs against injection with it. He cultivated it by the method of Inada and Ido, the original discoverers of *L. icterohæmorrhagæ*.

Noguchi then carried out experiments to differentiate his *L. icteroides* from *L. icterohæmorrhagæ* and found that monovalent serums of each agglutinated the homologous organisms more strongly than the heterologous, but that distinct cross-agglutination occurred—an indication of their close relationship. Continuing his work Noguchi next prepared an antiserum from horses (recorded in the *Journal of Experimental Medicine*, 1921) and found that a dose of 1 c c of a 1 in 10,000 dilution protected guinea-pigs against 5000 minimal lethal doses of the organism.

Noguchi's work found apparent confirmation when in the same year, 1921, P. P. Grova, describing an outbreak of yellow fever at Vera Cruz, stated that he was able to infect guinea-pigs by intraperitoneal inoculation of the blood of patients, to obtain cultures of *L. icteroides* from these animals and with them infect others—all dying with symptoms of yellow fever. Further, Noguchi, with Khigler, isolated a strain of his *Leptospira* from a case of yellow fever in Peru.

In the *American Journal of Hygiene*, 1921, Noguchi published a general account of his work with photographs of his causative organism which seemed to differ in no respect from that discovered by Stimson in 1905 in the kidney of a yellow-fever patient and called by him provisionally *Spirochæta interrogans*, as he was uncertain of its nature [This is a peculiar use of the participial adjective and does not tell us what the Spirochæte was 'asking'—presumably to be recognized]

In 1923 Noguchi continued to record good results with his horse-prepared serum, used both prophylactically and therapeutically. Thus, at Tuxpan, Mexico, of fifty-nine patients treated in the first three days of illness four died and to three of these only small doses had been given, from the fourth day onwards of illness the effects were not good. Among ninety-five patients receiving the serum on or before the third day the fatality rate was 13.6 per cent, among the untreated [the number is not given] 56.4 per cent, or more than four times as great. As regards its use prophylactically, in Salvador, of a non-immune population of about 113,000, two injections were given to 3607 and among these no case occurred, but among the uninoculated the incidence was 1.6 per mille. In Tuxpan cases occurred among the vaccinated in the first two weeks (that is, they were probably vaccinated during the incubation period), but none later, although the outbreak continued unabated. Noguchi stated that the vaccine does not become effective till about ten days after the second injection.

Noguchi was now at the zenith of his reputation, the following year doubts began to arise. W. H. Hoffmann of Havana experimented with Noguchi's organism and with *Leptospira icterohæmorrhagica* and he found that the lesions produced by the former were closely similar to, in fact to him indistinguishable from, those set up by the latter. Prior to this, in 1922, P. H. Manson-Bahr, C. M. Wenyon and H. C. Brown had found that serum from a convalescent case of Weil's disease gave equal protection against both *L. icteroides* and *L. icterohæmorrhagica*. The natural questions followed, first, Was there a *L. icteroides* different from *L. icterohæmorrhagica*? Second, if so, how could they be distinguished? Third, if not, had it any ætiological relation with yellow fever? Fourthly, were not the patients in whom the leptospira had been found suffering, not from yellow fever, but from Weil's disease? Lastly, what was the value (or validity) of the beneficial results recorded from the use of the antileptospira serum, either prophylactically or therapeutically?

In 1925 came a recrudescence of favourable reports. Studies

carried out by Noguchi and others in Northern Brazil, constituting a combined Commission of the Rockefeller Foundation and the Brazilian workers led to the isolation of two strains of *L ictteroides*, and the serum of recovered patients agglutinated the organism and 0.001 c c of an anti-ictteroides serum proved protective to guinea-pigs against a thousand minimal lethal doses of the Brazilian strain. Further, in an outbreak at Belize, British Honduras, in a college of a hundred or more students, seventeen patients received the serum. Thirteen who were treated with it on the first or second day of illness recovered, the other four who did not receive it till the fourth day or later all died. Prophylactically, between one and two hundred susceptible whites in the town were inoculated with the vaccine and among them no cases were seen, two who had declined inoculation both contracted the disease.

This, however, was but a flash in the pan. In 1926 in a paper in the *American Journal of Tropical Medicine*, M. Theiler and A. W. Sellards threw doubt on the aetiological relationship of *L ictteroides* and yellow fever. Noguchi had laid much stress on the Pfeiffer reaction as indicating the causal status of his *Leptospira* and these two workers showed by means of this reaction the serological identity of this organism with *L ictero-hæmorrhagiae*, and further Sellards recorded in the same journal the following year that he had examined sera from eleven recovered yellow-fever patients, three and a half months after their illnesses, and found that the Pfeiffer reaction was negative against both organisms. It is well known that Weil's disease occurs in tropical America and in severe infections is difficult to distinguish, on clinical grounds, from yellow fever, hence, as stated earlier, it is probable that Noguchi obtained his organism originally, that called by him *L ictteroides*, from a case of infectious jaundice which had been mistaken for one of yellow fever.

Still further confirmation of this, and a further blow to the *Leptospira ictteroides*, came from attempts to convey it by *Aedes ægypti*. These were quite unsuccessful and it was found that, if ingested, the organism gradually disappeared.

In 1925 Andrew Connal of the Yaba Research Institute, Lagos, Nigeria, made several attempts to transmit the disease to guinea-pigs, but without success. Five c c of blood taken on the second, third and sixth days of disease were inoculated intraperitoneally but with entirely negative results. Also, *Aedes* were allowed to suck the blood of patients during the first three days of illness and were kept alive for many days, being fed on guinea-pigs, but all the animals remained alive and well. No *Leptospiræ* were

found in the blood or urine of cases of yellow fever studied by Connal, nor were any discovered in the organs of fatal cases. The experience of Dr W A Young (who died from yellow fever on 30th May, 1928) and his colleagues at Kura in the Gold Coast was the same—they did not succeed either in infecting guinea-pigs or in finding leptospiræ.

In 1929 Sellards repeated some of Noguchi's former work and examined yellow-fever (true yellow fever) patients but was unable to find a *Leptospira* in the blood and moreover he obtained no agglutination of it with the serum of convalescing patients. The last nail in the coffin of *Leptospira ictteroides* may be said to have been driven in by Noguchi himself who went to West Africa full of hope and enthusiasm to prove his case, but failed to find the organism in the patients there. Noguchi died in West Africa in 1928 from disappointment and yellow fever. In the obituary notice of Noguchi to be found at the end of the report of the Dakar Conference, March 1929, occurs the following

Inspector-General Lasnet, on his return from a mission in the Congo, stopped *en route* at Kura at the end of March to call upon Noguchi. Professor Noguchi told him frankly that he too had been unable to find any further trace of *Leptospira ictteroides*, and that it would no longer be possible to consider this the specific agent of the African disease.

Hideyo Noguchi was a great man—mentally, for physically he was short of stature—and his many successful researches have been swamped by his last great mistake. There are no supporters now of his claim that *L ictteroides* is the causal agent of yellow fever, nevertheless, let it not be said of him that there is

None so poor to do him reverence

At the risk of being charged with vain repetition, the details of his experiments, now forgotten by many of us, are worth recalling briefly, because, as set out by him, they led him step by step onwards and appeared most clear and convincing.

When, as a member of the Yellow Fever Commission of the International Health Board, he was studying the disease in Guayaquil, in conjunction with Dr Wenceslas Pareja who was in charge of the Yellow Fever Hospital, he analysed the symptoms of 172 patients and inoculated guinea-pigs with the blood of twenty-seven. The blood, he stated, was drawn from patients admitted to hospital while he was there and injected directly before coagulation, into the peritoneal cavities of the guinea-pigs, and he recorded that "of seventy-four guinea-pigs inoculated with

specimens of blood from twenty-seven cases of yellow fever, eight, representing six cases, came down with symptoms resembling yellow fever "

In the first case the inoculations were made on 14th July, 1918 Two guinea-pigs inoculated with blood collected on the sixth day of illness became ill, but recovered , some of the patient's blood which had been put into culture medium was kept for three days and then injected into two more guinea-pigs Both died with the usual signs of leptospirosis and *Leptospiræ* were found in the organs of one of them and also in a passage guinea-pig inoculated from the other

In a second case, a guinea-pig was inoculated with 4 c c of a patient's blood, collected on the fourth day of illness The animal developed fever and became jaundiced , it was killed six days later and other guinea-pigs inoculated with its blood became ill in the same way In a third case similar results were obtained

The fourth case is of particular interest because leptospiræ were cultivated directly from the patient's blood and were found in his liver when he died on the fifth day of his illness A guinea-pig inoculated with blood collected on the third day died twelve days later with *Leptospira* in its blood In the fifth case leptospiræ were found in the liver and kidneys of a guinea-pig inoculated with the blood of a patient on the sixth day of illness, and a pure culture was obtained A sixth case gave results similar to those of the fourth detailed above Noguchi adds that abortive symptoms were observed in twenty-one other guinea-pigs out of seventy-four inoculated with blood from the twenty-seven patients, and in many of these there was a subsequent immunity to inoculation with leptospiræ

In August the same year Noguchi carried out transmission experiments with mosquitoes He made six attempts to convey the disease from yellow-fever patients to guinea-pigs by the bite of *Aedes ægypti* , only one attempt was successful In this instance forty recently hatched female mosquitoes were fed on a patient who had been ill for three days , five days later sixteen of them were allowed to feed on a guinea-pig The animal remained healthy Eight of the mosquitoes which were still alive twenty-three days after their first feed were then allowed to suck the blood of a second guinea-pig , this animal died jaundiced in seven days A third guinea-pig inoculated from the second died with similar symptoms and leptospiræ were found in its blood

Noguchi next attempted to convey the disease from guinea-pig to guinea-pig by the agency of the mosquito and was successful

in two attempts out of seven. In the first a healthy guinea-pig was bitten by mosquitoes twelve days after they had fed on a guinea-pig with leptospiræ in its blood, the test animal died of leptospirosis. In the second successful experiment eighty-three *Aedes* were allowed to bite a healthy guinea-pig eight days after they had fed on one which was infected, the test animal died thirteen days later and leptospiræ were found in its blood and organs. Twenty-five of this batch of *Aedes* were emulsified in a mortar ten days after their first feed, a few leptospiræ were found in the emulsion and when it was smeared on the scarified skin of a guinea-pig it produced the disease and the animal's blood contained the organisms.

Noguchi's claims at this stage may be thus summarized. A disease resembling yellow fever was produced in guinea-pigs by inoculating them with the blood of persons suffering from the disease. Leptospiræ were found in the blood and organs of the infected guinea-pigs, and these organisms were cultivated and when inoculated reproduced the disease in other guinea-pigs. Leptospiræ were cultivated direct from the blood in three cases of yellow fever and they were found in the liver of one patient who died of the disease. The infection was conveyed from a yellow-fever patient to a guinea-pig by the bite of mosquitoes and leptospiræ were found in its blood. The disease was also conveyed from infected to healthy guinea-pigs by the agency of the mosquito, but not earlier than the eighth day after the first feed. Finally, leptospiræ were found in crushed *Aedes ægypti* ten days after feeding on an infected guinea-pig and the disease was reproduced in a test animal by smearing the emulsified mosquitoes on its scarified skin.

[It will be remembered (see p. 388) that Sellards was unable to convey either *L. icteroides* or *L. icterohæmorrhagiæ* from man to guinea-pig or from guinea-pig to guinea-pig by means of mosquitoes. Also W. Schuffner reared large numbers of *Aedes ægypti* in Amsterdam from eggs sent to him from Cuba by Professor Hoffmann. He allowed 350 of these mosquitoes to bite guinea-pigs infected with *L. icteroides* and subsequently fed them on healthy guinea-pigs, but no infection resulted. He repeated the experiment with guinea-pigs infected with *L. icterohæmorrhagiæ*, the results were the same—negative.]

Noguchi proceeded to clinch the proof of the connection between *Leptospira icteroides* and yellow fever by a series of Pfeiffer reactions with the blood of convalescent patients added to emulsions of the livers of guinea-pigs which had died from the disease. His results

were positive, the organisms were agglutinated and the test animals protected, whereas in the control animals the reaction was negative and the animals died [As we saw above, Sellards carried out the test with the serum of convalescent yellow-fever patients in Parahyba, but found the reaction negative and no protection conferred against either *Leptospira*]

Noguchi's next step was to carry out immunological studies with *L ictroides* and *L ictero hæmorrhagæ* by means of mono-valent sera produced by intravenous inoculation of rabbits and he showed to his satisfaction that by agglutination tests, by Pfeiffer's phenomenon, by complement fixation and by protective experiments, that the two *Leptospiræ* were distinct, the *L ictroides* from the *L ictero hæmorrhagæ*, the organism of infective jaundice, though

There exists [he writes] an undeniable though feeble cross-protective reaction which may be explained by assuming that the two groups of organisms are not altogether alien but are closely related to each other, they may even constitute two sub-species or races

In 1928, C Margarios Torres reported finding oxychromatic degeneration of liver cells with development of acidophile intranuclear inclusions in cases of fatal yellow fever in monkeys and he concluded that yellow fever was caused by a filtrable virus producing intranuclear inclusions as in herpes zoster, varicella, and virus III of rabbits. He noted that these differed somewhat in size and number in monkeys, *Macacus rhesus*, according as they were infected with the African or Brazilian strain, the fragmentation being more marked in the former. Though they were seen in monkeys infected by blood from human cases, Torres did not find them in fatal cases in man and interpreted this as due to disappearance of the virus from the blood and organs before death. Subsequently, he reported a successful search for them in a patient dying about forty hours after the onset of symptoms. To demonstrate them special staining, as by Goodpasture's method for Negri bodies, is necessary, when the inclusions are coloured a blue-violet while the nucleolar fragments are red. E V Cowdry and S F Kitchen also gave a detailed account of these inclusions and compared them with those of herpes, varicella and virus III. O Penna and de Figueiredo of the Oswaldo Cruz Institute, Rio de Janeiro, agreed in their being a pathognomonic sign for the diagnosis of yellow fever, but they ascribe the priority of description, not to Torres, but to Councilman. E C Smith in West Africa also found them in thirty-nine out of forty *rhesus* infected with yellow

fever, but in none of ten normal monkeys, and in fifteen out of twenty-two human cases—a far higher proportion than in Brazilian cases

During the ensuing year the virus idea came more prominently to the front Nicolau, Kopciowska, Mathis and others found inclusion bodies in the nuclei of the nerve cells of the brain, in the Purkinje cells of the cerebellum, and exceptionally in the glial cells of the cord Then they were noted as present in other virus diseases and the interpretation offered was that the virus causes in cells which have succumbed to its action oxyphilic degeneration of the nucleus involving the whole of the chromatin which forms irregular masses, often peripherally distributed Nicolau and Mathis found that degeneration of this type might be produced in the liver of experimental animals by inoculation of toxin, for example of tuberculin or of *Vibrio septique* Later, they pointed out that the intranuclear inclusions in the nerve cells of guinea-pigs and mice experimentally infected with neurotropic yellow fever virus are to be distinguished from oxyphile degeneration of the nucleus resulting from injury to or death of the cell The true inclusion bodies, ranging from 1 to 4 microns in diameter and usually more than one in a cell, are the response of the nucleus to invasion by the virus, each particle being enclosed by an envelope, as it were, set up by the reactionary effort of the cell to prevent its multiplication Such could be seen not only in the nerve cells, but other ectodermal cells, and in the liver We thus have passed from the stage of regarding the inclusions as the cause of yellow fever to that of reaction on the part of the cell to the cause which is of the nature of a virus, and this we must now consider in its historical bearings

We have seen (see p 384) that the causal agent of yellow fever is filtrable or ultra-microscopic, that is, it is a virus Of the virus itself there is not much to say, the importance of its application is both great and manifold and the basis of modern development and recent research It appears to be one of the smallest of known viruses, by the new high-speed vacuum centrifuge described by J H Bauer and E G Pickels it can be spun down, and according to Findlay and Brown the size of the particles is 17–28 $\mu\mu$

The virus has been said to bear certain resemblances to that of Rift Valley fever, but there are marked differences The size of the particles of the latter is half as large again as that of the former, sheep, goats, cattle and many small rodents are suscep-

tible to the Rift Valley fever virus, not to yellow fever, there is no cross-immunity between them, monkeys recovered from Rift Valley fever are susceptible to yellow fever and *vice versa*, and there is on record the case of a laboratory assistant who suffered from yellow fever in 1931 and three years later from Rift Valley fever, the virus being obtained from his blood on each occasion. Clinically and pathologically the symptoms are alike, both can give neurotropic strains and both are transmitted by *Aedes*. Pestana of São Paulo believes that though they are now distinct the two viruses had a common origin.

In 1927 A. Stokes, J. H. Bauer and N. P. Hudson inoculated Indian crown monkeys, *Macacus sinicus*, with blood from patients suffering from yellow fever, and these developed fatal yellow fever. Later, *M. rhesus*, a monkey more easily procurable, was found to be equally, perhaps even more readily, susceptible and the infection was carried on from monkey to monkey by inoculation of the blood or serum and also was transmitted from monkey to monkey by the *Aedes aegypti*. The serum of the monkeys was infective even after being filtered through V and N Berkefeld filters or through Seitz asbestos filters. The same investigators found also that 0.1 c.c. of serum from a convalescent patient would protect monkeys against otherwise fatal doses of infected blood and also against the bites of infected mosquitoes. Adrian Stokes injected a *rhesus* monkey with blood from a patient in the first three days of illness and when the animal died called in Dr. O'Brien, who had had experience of the disease in the Gold Coast, to see the post mortem, the latter confirmed the findings as typical of what was seen in human patients, leading Stokes to exclaim, "We have hooked the fish, now to land it!" Stokes died of yellow fever soon afterwards and it is generally believed that he infected himself when carrying out a post-mortem examination on an infected monkey. It would seem that monkeys remain infective longer than human beings and even till death and after, whereas man is supposed not to be infective after three or perhaps four days. On the other hand, it must be noted that whereas human patients rarely died before the fifth or sixth day of fever, monkeys commonly die before the fourth day.

The importance of the infectability of monkeys can hardly be exaggerated, the ability to infect an animal readily procurable and fairly cheap opened up the possibility of extensive research of which full advantage has been taken.

In 1928 Sellards and Hindle showed that the virus could be preserved in a frozen state. Monkeys were inoculated with blood

from a yellow-fever patient at Dakar and others by mosquito transmission. A monkey was killed at the height of the infection, the liver removed and frozen at once and kept at low temperature during a twelve-day journey to London. Here a monkey was inoculated with an emulsion of the frozen liver and contracted the disease and, in fact died of it (see later, p 403). Next, Hindle demonstrated that the infective properties were retained if the liver were dried *in vacuo*, and in 1929 W A Sawyer, W D Lloyd and S F Kitchen wrote an article giving detailed accounts of experiments on the various methods of preserving the virus. They found that better preservation was obtained by freezing the material prior to drying *in vacuo*, also that the virus in 50 per cent glycerin retained its potency for at least sixty days if stored in a refrigerator, but lost it in a hundred days. Pettit, Stefanopoulo and Kolochine recommended Vallé's glycerin-phosphate mixture for preservation of the virus in infected blood or liver, in the refrigerator, and Sawyer and Frobisher found that the virus in the mosquito, if suspended in saline, is arrested by Berkefeld V and N candles, but that it becomes filtrable if an equal volume of normal serum from the monkey is added.

The amount of virus contained in an infected monkey is great, Bauer in 1931 showed that the blood might contain a thousand million lethal doses per c.c., moreover, the virus could pass Chamberland L II candles in undiminished concentration. Further study of the virus by Hindle and Findlay showed that the virus is negatively charged at pH 5.2-7.0 and is destroyed by acid media of pH 3.0-4.0.

Loring Whitman has demonstrated the multiplication of the virus in the transmitting mosquito. He did this by feeding *Aedes aegypti* on monkeys with the Asibi strain of yellow fever and testing, with mice, the amount of virus present after varying intervals. After the ingestion of infected blood the virus content fell for some days to a minimum in a week or so, then came a rapid increase. One example may be quoted.

Time after feeding	Titre with thirty mosquitoes
0 days	22,000
3 "	900
10 "	16,000
24 "	24,800
38 "	1,275,000

The discovery of *rhesus* susceptibility enabled trial to be made as to whether other vectors than *Aedes aegypti* might exist. Though not proved to be vectors in nature several insects have been found

capable under experimental conditions of conveying infection, among them *Aedes luteocephalus*, *Aed africanus*, *Aed vittatus*, *Aed simpsoni*, *Aed serratus*, *Aedimorphus apicoannulatus*, *Tænorhynchus* (*Mansonioides*) *africanus* and *Eretmopodites erythrogaster*. *T africanus* is ubiquitous and, judged by the precipitation test, seems to feed voraciously on man. Loring Whitman and Antunes, in 1937, found that *Aedes scapularis* and *Aed fluviatilis* were efficient vectors of the virus.

Aedes geniculatus, a common mosquito in Europe, breeding exclusively and, during the summer, feeding readily on human beings, has been shown by Roubaud and his co-workers to be an efficient carrier and transmitter of the yellow-fever virus (*Compt Rendu Acad Sci*, July 1937). Eight of them newly emerged were collected in Normandy and allowed to feed on an infected monkey. They were then kept for fourteen days at 30°–35° C, being fed on sugar. They then conveyed the disease to a normal monkey by their bite. Others, ground up and inoculated intra-cerebrally into mice, caused death from yellow fever encephalitis.

Other species, though they do not transmit the disease, even experimentally, by their bite, retain the virus for a considerable time and can by injection set up infection. Among these may be mentioned *Aedes nubilis*, *Aed terreus*, *Mansonia justamansonia*, *M fasciolata*, *M chrysonotum* and *M albicosta*, which were found to retain the virus in their bodies for long periods.

Another great step in advance for the study of the virus was made when in 1930 Max Theiler experimented by injecting the virus into the brains of white mice and found that they died with encephalitis but showed no jaundice or changes in the liver. He found that after several passages in succession in this way a 'neurotropic' strain of virus was developed. Later, in 1933, attempts were made similarly with guinea-pigs, but, though this animal was found to be susceptible, the virus was not maintained, as in the mouse, by brain to brain passage. If this neurotropic strain from mice be injected into the brain of a *rhesus* monkey this animal also dies of encephalitis without jaundice or hepatic lesions. Yet, further, if this virus is injected subcutaneously into a monkey no obvious reaction occurs, nevertheless the animal acquires immunity (see later). As with monkeys, so in man this virus was found to have lost all power to set up visible reaction, yet if injected with convalescent patient's serum immunity resulted. This is not merely an academic matter, it enabled investigators to work with the virus without risk.

7 IMMUNITY, AND THE EMPLOYMENT OF IMMUNITY TESTS FOR DETERMINING THE DISTRIBUTION OF YELLOW FEVER

The question of immunity in relation to yellow fever concerns, of course, the serologist and immunologist in particular, but since it has also some historical interest it must be briefly touched upon.

Whether there exists any congenital immunity due to peculiarities of race is doubtful, it is not always easy to exclude 'acclimatization fever' and infection in childhood. In the outbreak of 1852-3 the fact was noted that in Guiana African immigrants escaped, but we must not forget that these immigrants had come from West Africa. It would seem that admixture of negro with white blood does render the subject more susceptible, thus the infection was observed to be more common among mulattoes, quadroons and octaroons than among pure negroes. Here, again, we must bear in mind that the former were born in America, not in Africa. Others go further and state that the negro in America—that is, the American-born negro—seems to possess a true racial resistance, because, though not previously exposed, when an outbreak occurs, the negroes suffer less severely than the whites, at least in the Southern United States, that is, he is more resistant to the *toxin*, not to *infection* itself. H. R. Carter believes that yellow fever is propagated mainly in the natives and especially in the children, but is noted only when susceptible whites are exposed to infection. In brief, all races would seem to be equally susceptible to infection—Chinese, Indians and Europeans. Dr. Carter wrote in 1931 "even the African negro contracts yellow fever as readily as other races, but he has it in a milder form and death from it among them is rare." Japanese and Chinese show a fatality rate equal to that of Europeans. This view of equal susceptibility was generally believed, but in the outbreak in Rio de Janeiro in 1928-9 the South American black races showed a lower incidence than did the whites.

On the other hand, records show that the black races are not immune unless living in an endemic area. In Barbados, for example, they often suffered equally with the whites when infection was freshly introduced after an interval during which non-immune natives increased in number. So we find that white people born in yellow-fever countries and surviving the period of childhood often exhibit resistance (or immunity) to yellow fever, while native, coloured races, not inhabitants of yellow-fever countries, are susceptible, though, as already mentioned, even in them the course is often milder. That these views are, in general,

correct, or at all events safe enough in practice, the following more concrete evidence may be adduced. Carter writing in 1916 stated that between 1888 and 1898 over 30,000 persons entered the ports of Florida certified as "Protected from yellow fever by previous attack or by two years' residence in an infected focus." They came, between May and October, from Havana where the disease prevailed at the time to Key West—an eight-hour journey—and Tampa—twenty-four hours—in both of which places there were many susceptibles and *Aedes* in abundance. Nevertheless, there was no outbreak in Florida during that period and no second attacks among the immigrants. There were, however, 450 persons from Havana in quarantine because they did not satisfy the above requirements, among these there were thirteen cases.

The fact that there were no cases among those certified and admitted or among the non-immune residents points to the unlikelihood of these being carriers of infection. It may be added that of recent years, that is, prior to 1916 when Carter wrote, quarantine stations of the United States had passed in well over a hundred thousand persons from yellow-fever ports, but there was no evidence of their having infected *Aedes* in the States.

The uncertainty of the degrees of racial susceptibility depends largely on the difficulty of diagnosing mild cases (prior to the mouse-protection test). H. Beeuwkes, J. H. Bauer and A. F. Mahaffy proved, by this protection test (see later) the existence of yellow fever in several large towns, although they were unable to identify clinically actual cases among the native population. Again, in Guayaquil in 1918 and in the Rio de Janeiro outbreak later Weil's disease and other causes of jaundice might be co-existent with true yellow fever, also, as we have seen (p. 321) in Nigeria there is an unnamed disease associated with jaundice and a symptomatology remarkably suggestive of yellow fever. It was because of this difficulty in deciding whether a patient was suffering from true yellow fever in a mild form or some other disease that Lasnet suggested at the Dakar Yellow Fever Conference in 1928 the term 'prophylactic diagnosis' for patients exhibiting fever and early albuminuria.

Another common belief with a certain amount of evidence in its favour is that known as '*immunité de séjour*' (residential immunity) in Europeans, that is, length of residence in an endemic focus bringing less likelihood of contraction of the disease. This, however, has not yet been proved, and if it is a fact it is not, it would appear from the protection test, ascribable to the presence of antibodies, in other words, to a mild or overlooked attack.

Hastings was a strong upholder of the possibility of second attacks, nay more, of their probability if the subject remained in the country where he was first attacked—at variance with almost all other writers who maintained that one attack protected for life and that the subject could remain with impunity in an endemic centre. Hastings is so certain and, to avoid any misconception, we quote his own words: “In the past summer in the Gulf of Mexico I saw more than two hundred such cases.” He is “fully aware of the great weight of authority against this view, yet, with all deference, modesty should never have the effect of hiding truth.” He quotes letters from fellow-officers in the United States Navy recording second attacks. Thus, Lieut J R Mitchell, U S Navy, writes

I had an attack of yellow fever in Charleston, South Carolina, in the memorable summer of 1817, when it raged with the greatest virulence. I had a second attack in 1821 in the small town of Jackson, Alabama, when the fever prevailed as an epidemic in its worst form. My case was for a time regarded as hopeless. In the summer of 1822 I had another (the third) attack in Pensacola, where the disease of a most malignant type prevailed, and I distinctly remember that this attack was quite [as], if not more violent than, the generality of those cases which proved fatal.

Again, in a letter dated 25th March, 1848, Dr T M Potter, U S Navy, who had had ample opportunities of acquiring knowledge of the disease, states: “I can also agree with you fully in the frequent recurrence of the disease.” [See also p 334, the epidemic of 1796.]

E Hindle was the first to suggest and prepare prophylactic vaccine made of the emulsified liver and spleen of infected monkeys, on the lines adopted for fowl plague, dog distemper and foot-and-mouth disease, and to show its effects in experimental animals, in 1928. Since then much has been done. In 1932 Sawyer introduced sero-vaccination, that is, injection of immune serum together with living virus, primarily his object was to put a stop to a series of accidental laboratory infections. This was no small risk, A W Burke and N C Davis record (*American Journal of Tropical Medicine*, 1930) three certain laboratory infections and a fourth probable case, in Bahia, Brazil. One was infected by the bite of a mosquito, one probably when performing an autopsy on a monkey (as Stokes in Africa), and two through contact with the blood of infected animals. G C Low and N H Fairley showed (*British Medical Journal*, January 1931) that grave danger may be entailed in the routine collection and examination of human

blood in yellow fever Three cases occurred in the laboratory of the Hospital for Tropical Diseases, London One presumably became infected through handling yellow-fever monkeys, the virus (Brazilian) having been passaged through monkeys for a year, thus clearly proving that such passage does not lessen its virulence for man The other two did not come into contact, directly or indirectly, with infected animals, one was engaged in making blood-smears and carrying out a leucocyte count, the other in routine biochemistry on a specimen of blood sent to the laboratory One of these patients died This indicates that in endemic areas gloves should be worn by those taking blood specimens, whether yellow fever is suspected or not

Because blood retains its infectivity and can therefore be sent to a distant laboratory for diagnosis to be made, or a provisional diagnosis confirmed, there is, as is shown by the above cases, no little risk to laboratory workers, and particularly in countries where *Aedes* is abundant It is on this account that some countries, Dutch East Indies, India and the Belgian Congo, have forbidden the introduction of, or working with material containing or suspected to contain the virus of yellow fever

In recent years intense laboratory studies have been undertaken with a view to obtaining a virus biologically attenuated for use in human immunization It was for some time held that the virus obtained from cases in South American ports was not so highly pathogenic for Europeans as that from West Africa It is true that differences in pathogenicity for animals do exist It is possible that differences may be found between strains usually transmitted by *Aedes aegypti* in towns and others, in a manner analogous to the virus of Rocky Mountain fever transmitted by ticks, the Montana type transmitted by *Dermacentor venustus* being very fatal with a case mortality of perhaps 90 per cent, whereas in another place, Idaho, where the vector is *Dermacentor variabilis*, the fatality rate is only 5 per cent

Reverting again to the work of Theiler in 1930 It is a well-known fact that nervous symptoms are not by any means rare in the late stages of an attack of yellow fever, and ptosis, facial paralysis and optic atrophy are occasional sequelæ What Theiler showed was that the neurotropic potentialities of the virus could be enhanced till intracerebral inoculation of mice caused encephalomyelitis Animals early in series died on the seventh to the tenth day, later animals on the fourth or fifth, and after death the virus was found to be present in the central nervous system, the peripheral nerves and the suprarenals, but not in the blood Further

study has demonstrated that any strain of yellow-fever virus may be rendered neurotropic by repeated passage in the brains of mice, but the development to pure neurotropism and loss of viscerotropism is gradual

If the neurotropic virus is injected subcutaneously into human beings symptoms much less severe than those caused by the viscerotropic or pantropic virus are set up, but if the nervous tissues become infected encephalomyelitis occurs. A pantropic virus is one which produces lesions in tissues developed from all three embryonic layers. The neurotropic virus appears to be fixed, but in 1935 Findlay and Clarke succeeded in reconverting it into the pantropic, with gradual reduction of the neurotropism, by inoculating *rhesus* monkeys in series intrahepatically. The same year Hoskins found that whereas subcutaneous inoculation of monkeys with viscerotropic (pantropic) virus caused death, injection of mixed neurotropic and pantropic did not. This fact—that in general the neurotropic virus protects against the viscerotropic when the mixture is injected subcutaneously—was confirmed by Findlay and Mahaffy. Perhaps under normal conditions, certain virus particles have marked neurotropic potentialities, the result of spontaneous mutation, but these are in abeyance provided the virus does not invade a non-immune central nervous system. If this occurs multiplication of the particles with neurotropic potentialities takes place.

A killed virus, neurotropic or otherwise, seems to confer or give rise to no immunity, but a living neurotropic virus in so small a dose as 0.5 c.c. of a 1 in 1,000,000 followed later by 1.0 c.c. of 1 in 10,000 proves very effectually protective in man. In 1934 Laigret vaccinated over 3000 volunteers in Senegal and has since recorded that some 200,000 have now been vaccinated, without a fatality, though four or five have exhibited serious meningeal reactions all eventually recovered.

To recapitulate briefly. Four methods of immunization have been tried. First, inoculation of vaccine using killed or attenuated virus. This has not proved very successful. Second, inoculation of a biologically modified virus, as mouse virus, not used alone. Third, injection of immune serum, this is difficult to obtain in any quantity and protects but for a short time, three to four weeks. The difficulty, of course, is to obtain sufficient human immune serum, this may be overcome if the claims of Pettit, Stefanopoulo and Fraser that monkey serum, and of Charpenel, Mathis and Kolochine that horse immune serum will both neutralize the

mouse virus used are substantiated. Fourth, inoculation of a mixture, especially the biologically modified mouse virus, with immune serum. This is the most successful and the method in general use till a year or so ago. The use of a chicken virus has of late been employed, but some disasters have followed its employment, certainly a considerable time after, usually two to three months. It was not decided whether the vaccine was itself at fault, but caution was exercised and its use temporarily suspended.

The virus is cultivated by growing in embryo chicken tissue after removal of the head and spinal cord to prevent neurotropism. Even with this, severe jaundice has occurred, perhaps as long as eight months after inoculation, though usually in six to eight weeks. No satisfactory explanation has been found for the pathogenesis of this and only a proportion suffers. A group of 191 persons were vaccinated with two pools of monkey sera and culture virus at Campo Grande, Rio de Janeiro. Between two and eight months afterwards 61 of these (32 per cent) were more or less seriously ill with jaundice, but all recovered. As a contrast with this, 428 other persons were inoculated in Brazil with other pools of sera and 192 with one or more of the components of the virus at Campo Grande, but none of these showed any delayed jaundice (see also below, pp 409-10).

Laboratory workers with the virus are now so protected and also members of the services (civilians too if they wish) going out to countries where yellow fever is endemic. The duration of the immunity conferred, or acquired, in this way is not at present known. At first it was thought that, since an attack of yellow fever conferred lifelong immunity, so would such vaccination, expert opinion now, however, regards it as advisable for revaccination to be carried out in two or three years, or even less, one and a half to two years, if the serum on being retested is found to have lost its immunity.

A few more details on the methods employed for immunizing purposes will not be amiss, since they have now become of historic interest, though part of what we have to say is of a recapitulatory character.

Chronologically, pride of place must be given to Carlos Finlay who in 1881 attempted to immunize—and in his own view succeeded—susceptible persons against infection by subjecting them to the bites of mosquitoes which had previously fed on a yellow fever patient (see p 357).

Whether Freire came next, though nearly twenty years after, we are not certain because towards the end of the century the

bacteria idea of the causation of yellow fever was widely known and there was, as we have seen, more than one competitor for aetiological honours. Freire claimed that by injection of an attenuated form of the yellow-fever micrococcus—an organism of diameter $0.5-0.7\mu$ —into between 10,000 and 11,000 persons, he had succeeded in reducing the mortality of the disease by 90 per cent (pp 353, 381).

We have not been able to find any record of the use of Sanarelli's *Bacillus icteroides* as an immunizing agent, or prophylactic, though he prepared a serum from horses and reported good results from its employment therapeutically in 1898 (p 380). This was evidently considered by the United States Commission of 1899, for in their report occurs the following

The actions of serums may be divided into three classes (1) Those which prevent infection by stimulating the leucocytes to increased activity against the living germ (phagocytosis) (2) Those which, in addition, stimulate the whole cell economy to produce an antitoxin, or supply in themselves an antitoxin for the neutralization of the toxins produced by growing and multiplying organisms (3) Those whose power is exercised directly upon the micro-organism itself, having no power to stimulate phagocytosis or to supply or cause the elaboration of an antitoxin—the so-called *alexins*. To this class must the *serum anti-maryl* be relegated.

After an interval of a little more than another twenty years, we find Noguchi recording good results (in 1923) from the use of his *Leptospira icteroides* antiserum prepared from the horse (p 387), when employed prophylactically on the inhabitants of Salvador and of Tuxpan. He speaks of vaccination, but he seems to be referring to his antiserum and not to a vaccine.

As stated above (p 399) Professor Edward Hindle was the first to prepare on scientific lines a vaccine intended for immunization—for use prophylactically. Sellards and Hindle had shown that yellow-fever virus would tolerate transmission and retain potency for a period up to eighteen days, in a liver kept frozen in a mixture of ice and salt. From a liver thus brought by Sellards from Dakar Hindle prepared a phenol-glycerin vaccine which protected monkeys against over a thousand lethal doses of virus. Hindle found that infected organs when kept on ice gradually lose virulence and then are capable of acting as vaccines, dried virus when exposed to moist air acts similarly. The efficacy of a vaccine so prepared will depend naturally on the amount of virus present and Hindle does not regard a vaccine as efficient unless $\frac{1}{10,000}$ gramme produces infection, that is, 1 gramme contains 10,000 lethal doses for a non-immune *chæsus* monkey. He prepared the

vaccine by grinding with 9 per cent sodium chloride and after keeping it for some time in the ice-chest added sufficient water to reduce the salt concentration to 0.9 per cent. This sudden change in osmotic pressure causes swelling and rupture of the cells with liberation of the contained virus—the method of cytolysis. Formalin is added, two parts per thousand to a 20 per cent suspension of the organ tissue. To test it 1 c.c. of the vaccine is injected and ten days later a thousand m.l.d. of virus. Probably a longer interval would allow of a fuller development of immunity. It is of incidental interest to note that Hindle and his laboratory attendant both suffered from a febrile attack, temperature 104–105° F, lasting three or four days. This was regarded as influenzal as this disease was prevalent in London at the time, but afterwards it was found that the blood in each case was protective against infection. The attacks were, therefore, almost certainly mild yellow fever contracted in the laboratory (see p. 399).

The researches of H. de Beaurepaire Aragão on the Brazilian yellow fever carried out at the Oswaldo Cruz Institute independently of, but contemporaneously with, those of Hindle were on similar lines. He attempted to infect by inoculation four species of monkey, three *Macacus*, namely, *M. rhesus*, *M. cynomolgus*, and *M. speciosus*, and *Pseudocebus azaræ*. The first three were found susceptible to injection of the blood of human cases, of the blood and organ emulsions of infected monkeys and to the bites or emulsions of infected mosquitoes. By inoculation with blood of patients at different stages of illness he showed that infection in the blood-stream increases to a maximum in 24–48 hours and then declines, disappearing by the fourth day. Injection of emulsified mosquitoes is infective at any stage after they have bitten an infective patient (that is, on the first three days of fever), but the virus, though present in the body of the insect, does not reach the salivary glands till the ninth to twelfth days after feeding and hence does not infect by its bite till this interval has elapsed.

Aragão for purposes of diagnosis injected 2–4 c.c. of the serum of a convalescent patient (suspected of having had an attack of yellow fever) into a monkey and twenty-four hours later a lethal dose of the virus, its survival clinched a tentative diagnosis.

He also practised immunization of human subjects by (a) the serum of convalescents, 1–2 c.c., giving thus a rapid but transient protection. He employed it in sixty subjects without any ill effects. As human serum was not easy to obtain in quantity, he made attempts to immunize sheep and horses. (b) The vaccine of emulsified organs of infected monkeys—one part of organ

emulsion in five of diluent made up of 0.2 per cent formol in 0.5 per cent phenol, filtered through gauze and kept in an ice-chest for five days before being used. The dose for an adult was 2 c.c. subcutaneously. The reaction was said to be slight and less painful than Hindle's glycerin vaccine. Aragão tested it first on his laboratory staff and later on 300-400 persons in a small epidemic. None of those vaccinated contracted the disease.

By cross-immunity experiments he showed that the American and West African viruses were identical, thus confirming by modern scientific procedures what had been stated on grounds of clinical observation between eighty and ninety years before.

Though not part of the vaccine question, one more fact of importance may be conveniently mentioned here as arising out of work carried on at the Oswaldo Cruz Institute. It was found that inoculation of blood or organ emulsions—liver, spleen, kidney, bone-marrow or brain—of patients dead of yellow fever did not cause the death of non-immune animals, nor, if the animals were killed, did they present the lesions of yellow fever, in other words, the virus did not exist in the blood or organs of human subjects dead of the disease—confirmation of the non-infectivity after the third or fourth day. Monkeys, it will be remembered, are infective after death for the virus is thus obtained from the organs of an animal dying of yellow fever and it is probable that Stokes contracted the infection of which he died by performing a post mortem on an infected monkey.

Later, Aragão's method was to inject intramuscularly into the deltoid 3 c.c. of the mixed sera of four recovered patients and, six hours later, 2 c.c. of the same serum with 0.001 gm. of the fresh virulent brain of a camondongo (a Brazilian mouse or house rat) subcutaneously.

Pettit's method was to inject living neurotropic virus and a heterologous immune serum. Findlay gave, at first subcutaneously, later intradermally, a mixture of virus and immune serum (the dosage having been worked out first experimentally on monkeys). Laigret gave three inoculations of attenuated mouse virus in glycerin.

Subsequent to this came the use of the pantropic virus attenuated by culture on tissue, combined with immune serum, by 1936 it had been tried on nearly 400 persons in London, on 500 in Rio de Janeiro and thirty-five in New York. It had the advantage of not setting up any noticeable reaction. Drs. Sawyer and Bauer, of the Rockefeller Laboratory, New York, have succeeded in preparing a hyperimmune serum from *M. rhesus*, with

an activity twenty times on an average, and 60-80 times in some cases, that of human sera. This has been used on 535 persons and only one gave a severe reaction. This is very important because so much smaller doses are required and, as stated above, human serum in quantity is not easily procurable. Of course, artificial immunity is not so lasting as that resulting from an attack of the disease, which is believed to be lifelong, and it is, therefore, of the greatest use for safeguarding those going to the West Coast or other yellow-fever countries for a trip or a tour of service and those receiving it should be tested again in two years or so, if returning to the infected district, to see what degree of immunity remains and if it is much reduced revaccination should be undertaken.

The next point of historical interest is that of the progress which has been made in our knowledge of the virus, owing mainly to the work of F. L. Soper, C. M. Findlay, E. Hindle, Lloyd, Theiler, Ricci and Whitman. We need not repeat, beyond mentioning in passing, the finding of Stokes, Bauer and Hudson in 1927 that *M. sinicus* and, later, *rhesus* could readily be infected, or the mouse infection by Theiler in 1930. In 1933 Findlay and Brown demonstrated that the virus of yellow fever was one of the smaller filtrable viruses, and Findlay and Clarke in 1935 that the neurotropic virus could be converted into the viscerotropic by repeated intrahepatic inoculation and that, *vice versa*, the viscerotropic was convertible into the neurotropic by repeated intracerebral inoculation of monkeys. The same year Lloyd, Theiler and Ricci were able to cultivate the virus on special tissue media, and Whitman showed that it multiplies in *Aedes*. Susceptibility of hedgehogs (*Ermaceus*) was also demonstrated and this fact may prove of epidemiological importance, as evidence of a reservoir host other than the monkey. In the same year also transmission from monkey to monkey was effected in the laboratory by the agency of mosquitoes of the genus *Hæmagogus* which has a wide distribution and has been observed vigorously attacking man in rural districts where jungle yellow fever is endemic. This is a matter which will doubtless be earnestly followed up.

Still more recent developments (1937) have been successful cultivation of the virus *in vitro*, for purposes of immunization of man, and the results of its use have been, though it is early days to look for a definite pronouncement, good and the reactions minimal. In the search for suitable tissues for cultivation of the virus mouse embryos were inoculated and examination of their organs showed that the greatest concentration of the virus was in

the brain Next, it was found that unmodified strains of the virus were readily cultivated *in vitro* in a medium of minced mouse embryo brain and Tyrode solution containing 10 per cent normal serum of the monkey After twenty to twenty-five subcultures in this the strain became readily cultivable in whole mouse embryo tissues medium, and prolonged cultivation in mouse embryo brain medium increases the neurotropic properties of the virus It is curious to note that attempts at *in vitro* cultivation with monkey tissues yielded results entirely negative

We need not recapitulate the information already given (p 403 *et seq*) on the various vaccine preparations of Hindle, Aragão, Laigret and others Suffice it to add that Laigret in 1934 recorded good results from the use of living attenuated neurotropic virus, others, however, made trial of it but were not so successful and in fact considered it dangerous unless immune serum was simultaneously injected

Antisera of high titre were prepared by Pettit and Stefanopoulo from horses in 1932, by Hughes from young goats and by Whitman from rabbits in 1935

In the French West African colonies, by the end of 1935, mouse virus without serum had been used for 23,890 vaccinations Some of the subjects had suffered from mild disturbance six to eight days after the injection, others from symptoms of a more serious character some twelve to fifteen days after, and the latter were thought to be due, perhaps, to associated spontaneous mouse virus It was on account of this possible danger when a pantropic strain preserved by tissue culture was employed that Lloyd, Theiler and Ricci in 1936 substituted chicken embryo tissue With Tyrode solution growth was first obtained on chorio-allantoic membrane, then in embryo tissue after removal of the head and spinal cord—that is, taking away nervous tissue to prevent neurotropism—and using a viscerotropic virus Tyrode solution contained human serum, 10 per cent

With this vaccine cases of jaundice might occur, perhaps months later, and it was thought that the virus of catarrhal jaundice had at one time somehow obtained entry with the human serum used and that this was being injected with the yellow-fever virus [Jaundice had similarly been observed to follow the use of adult serum for prophylaxis of measles] The next step, therefore (in 1937), was to inactivate the serum to destroy such adventitious virus, if present This subject is of sufficient importance to warrant a little more detailed notice

At the end of 1937 Dr Findlay reported that nearly 600 persons

had been inoculated with attenuated tissue culture virus without added immune serum. One advantage of this virus is that it cannot, or can only very exceptionally and with difficulty, be cultivated in *Aedes ægypti* and is, therefore, not transmitted if a person recently vaccinated is bitten by a mosquito, and can thus be used with greater safety where *Aedes* prevails.

Jaundice as a late sequela of vaccination is of importance in the history of yellow fever prophylaxis. Among 2200 persons vaccinated, fifty-one cases of jaundice had occurred after an interval of two to six months, forty-six in Africa, five in England. The symptoms were distressing, though not fatal. They comprised general malaise, nausea, occasionally vomiting, temperature up to 100° F, deep jaundice in three or four days, bile in the urine, clay-coloured stools, slight enlargement of the liver, leucopenia with relative lymphocytosis. The jaundice might persist for weeks and it had followed injections of the neurotropic virus, tissue culture virus with or without added human, horse, or monkey immune yellow-fever sera.

There are several theories put forward to account for this late jaundice, the chief being

- 1 That it was due to *recrudescence or reactivation of the yellow-fever virus*. Against this were the facts that the symptoms were not those of yellow fever, the virus was not obtainable from the blood, and there was no rise in yellow fever immune body titre during or after the attack of jaundice.

- 2 That it was due to *infection with the virus of epidemic catarrhal jaundice*. This is not rarely present in man, but a proportion of 2-3 per cent of 2200 persons inoculated is beyond mere coincidence.

- 3 That it was due to *some hepatotoxic substance introduced with the inoculum*. This is very vague, no obvious toxic substance was introduced.

- 4 That the *virus of epidemic catarrhal jaundice had been introduced with the inoculum*, perhaps in the 'normal' human serum used for suspending the virus. To test this, all serum used for suspension or for tissue culture was inactivated by heating to 56° C for half an hour before use. Cases still occurred.

- 5 That the jaundice was *part of an anaphylactic syndrome*. Hughes in 1933 showed that a protein derived from the breaking down of tissues occurs in the blood in acute stages of yellow fever and that it is antigenic in the person from whom it is derived. It was possible that the reaction might occur between the immune body to this and fresh tissue break down products.

- 6 That injection of yellow-fever virus reduces resistance so

that any subsequent non-specific attack on the liver may damage that organ. Under such circumstances there would be reduction of the resistance against the virus of epidemic catarrhal jaundice, or an attack might be precipitated by malaria, by an operation, etc.

Let us turn to the question of vaccination against yellow fever in America. In December 1936, the virus employed was one which had been modified by successive mouse-brain passage given with human immune serum. Though good, its scope was limited by the difficulty of obtaining sufficient human immune serum. For this reason a virus cultivated in mouse embryo tissue was used together with immune serum obtained from animals, goats, horses, monkeys. Some of those inoculated presented severe reactions, others a late febrile reaction suggesting infection with the virus, others again developed no protection, while a fourth group suffered from an attack of jaundice, which might be severe, some four to eight months afterwards. Workers in America next employed the Asibi strain, as has been recorded above for England, cultivated in chicken embryo tissue after removal of the head and spinal cord, because an older virus cultivated on the whole tissue attained a high degree of neurotropism. This later virus no longer produced encephalitis when tested on monkeys although it conferred immunity.

The strain now used, known as Virus 17D, is of sufficient importance to warrant a little more detail. As stated above, it came originally from the Asibi strain. After many passages in *rhesus* monkeys it was established in tissue culture containing mouse embryonic tissues together with 10 per cent normal serum of the monkey in Tyrode solution. Eighteen such culture passages were made and subculture was then carried out in whole chick embryo, fifty-eight passages in series were made in this way, and it was then transferred to chicken embryo with the brain and cord removed with the purpose of excluding any neurotropic tendency as far as possible.

This vaccine was first used in Brazil in February 1937 on a small group of volunteers in the laboratory. These were found to have acquired immunity although their reactions were but mild—headache and influenza-like symptoms on the fifth to eighth day after vaccination, and these not severe enough to necessitate stopping ordinary routine duties. In June 1937 it was used for larger groups of persons in a rural area in Minas Geraes, and in the next month 761 were inoculated, and in a fortnight of August 1696. The following month field vaccination on a large scale was taken in

hand An early report in 1937 stated that more than 5000 persons had been vaccinated by this method in Brazil and about a thousand in Colombia Between February 1937, when it was first used tentatively, and January 1938, 59,532 had been vaccinated without mishap Later on in 1938 it was reported that there had been no instance of post-inoculation jaundice among 80,000 persons thus immunized in Brazil, whereas there had been 89 among 3100 inoculated with the British virus The strain hitherto used in England was then changed, and since the introduction of the new strain no further cases of this jaundice have been reported

A still later report received from Dr D B Wilson at Rio de Janeiro stated that by the end of September 1938 over 800,000 persons had been vaccinated in the nine months of the year

We have mentioned above the discovery of Max Theiler in 1930 that the virus injected into the brain of a mouse, or elsewhere if its action be directed to the brain by local injection of starch, for example, sets up an encephalitis or encephalo-myelitis (p 396) and that in time, by passage, the yellow-fever virus became a neurotropic virus from a viscerotropic or pantropic

The fact that the serum of a convalescent patient would counteract the lethal effect of the virus led first to testing the serum of a patient convalescent or recovered from an obscure fever by observing whether it protected a susceptible monkey against injection of a known yellow-fever virus or not In other words, instead of making a diagnosis by injecting into a susceptible monkey the blood of a patient with fever, in the early days of his illness—and, as we know, beyond the third day his blood is probably no longer infective—and noting whether the animal dies and exhibits the pathological lesions of yellow fever, the corollary of this test was employed for diagnosis by injecting a known virus, yellow fever, and noting whether the suspected patient's serum protected the non-immune animal or not This was an expensive method and when the application of Theiler's work showed that the results were equally reliable with mice, the diagnosis was facilitated by use of a procedure much less costly and the so-called 'Mouse protection test' came into wide practice

In 1930 H Beeuwkes, J H Bauer, and A F Mahaffy, members of the West African Yellow Fever Commission, were studying the endemicity of the disease by the monkey (*rhesus*) protection test In Ibadan and Ilorin regions of Southern Nigeria they found nearly one-third (30·4 per cent) of sera tested to be positive, but in Ife, where there had shortly before been an outbreak, 68 per cent were positive and practically one child in every four had a serum

which was protective. In the same year Theiler was carrying on his experiments. He found that in the early stages of intracerebral inoculation of mice with yellow-fever virus the incubation period ranged between eight and fourteen days, but that after fifty or more passages this was shortened and death occurred 51 days after inoculation. This result was, however, averted if immune monkey serum was injected at the same time. Human serum was found to be equally protective. He found also that the virus could be maintained indefinitely by brain to brain passage, with loss of virulence to monkeys and that the protective effect of yellow-fever serum could be demonstrated by injecting a mixture of immune serum and virus into the brains of mice.

We can now see what a wide vista this opened up. If an attack of yellow fever confers lifelong immunity to subsequent infection—and of this there is practically no question—and if the mouse protection test is specific and absolutely reliable—this unfortunately is not quite so certain—then a survey of a country can be undertaken and according to the results we can say whether or not there has been an outbreak of yellow fever, or that the disease has existed in a district within the lives of the inhabitants. We can not only test the diagnosis in a dubious case but we can determine the existence of past disease in a community. Let us see how this has been applied, but first we will briefly recapitulate and epitomize the course of the investigations which have brought us to this position.

Prior to 1930 the 'protection test' was performed by injecting 5 c c of the patient's serum into the peritoneal cavity of a *rhesus* monkey and four hours later 1 c c of a 1 in 10 dilution of virus, prepared from an infected monkey killed at the onset of fever. Survival of the animal confirmed the diagnosis.

In 1930 Max Theiler of Harvard found that if white mice are inoculated with yellow-fever virus intracerebrally, an encephalitis is produced and not the symptoms of yellow fever, although emulsion of the brain of a mouse so treated when injected into a *rhesus* monkey causes the symptoms of, and death with the lesions of yellow fever. If serum from a convalescent or recovered patient is injected with the virus into the mouse's brain, encephalitis is not caused, protection is afforded. This is the *intracerebral protection test in mice*. In 1932 W. A. Sawyer and W. Lloyd proposed a modification of this. 0.03 c c of a solution containing 2 per cent starch and 0.9 per cent NaCl is injected into the brain of a mouse, the object being to set up a mild irritant effect to localize the virus there. Next, a mixture of yellow-fever virus

(0.2 c.c.) and serum (0.4 c.c.) of the suspected patient is injected intraperitoneally (controls receiving the virus but no serum) and the animal is kept under observation for a fortnight. The controls die, the others survive if the serum was from a yellow-fever patient. This is the *intraperitoneal protection test in mice*. It is not only cheaper but better than the monkey test because it is possible that among the monkeys used one here and there may be found naturally resistant to infection. On the other hand, we cannot say that the mouse test has *no* exceptions, rarely, very rarely, anomalous results are observed, but we are in a position to affirm that a positive result is very strong evidence of previous infection. Hence, if *groups* of persons are tested these rare non-specific reactions are of less importance and we can derive valuable epidemiological information from the test.

From the epidemiological point of view the test is of service in four ways

- 1 To determine if yellow fever has been present in a region or district, and its extent. Thus, if in such an area the blood of many of the children is protective, there has been recently an extensive, though perhaps unsuspected epidemic, whereas if the blood of children is negative while that of adults is positive, it may be inferred that an outbreak had occurred in the past, but not within the preceding ten to twenty years.
- 2 To map out areas of endemicity, or the absence of it, and so to decide as to the necessity for control measures.
- 3 To identify or confirm the occurrence of yellow fever in areas where the disease is believed to be present, but is rarely or never recognized.
- 4 To determine if those who have been vaccinated against yellow fever by any method are in reality immune.

The Rockefeller Foundation has been of inestimable help in agreeing to train medical officers of colonial services in the performance of protection tests and to examine and test sera sent to their New York laboratory.

As an outcome of a Conference at Cape Town in 1932 an Immunity Survey of Africa was taken up and the preliminary findings confirm that the endemic area extends from Senegal to the Congo, while the area of 'recent infection' has the following boundaries. On the *north*, a line drawn from St. Louis, Senegal, to El Fasher, Dafur, in the Anglo-Egyptian Sudan, and thence

more southerly between El Obeid and Willing to a point east of the Nile. On the *east*, a line extending from the last directly south to the boundary of Uganda and the Sudan, then south-westerly through Usumbina at the northern tip of Lake Tanganyika to a point south and west of Albertville. On the *south*, a line from this last due west to the Atlantic just south of Santo Antonio de Zaire. On the *west*, the Atlantic Ocean.

In the area thus demarcated lie much of French West Africa, the Gambia, Portuguese Guinea, Liberia, the Gold Coast, Nigeria, French Cameroons, most of French Equatorial Africa, the south-western part of the Anglo-Egyptian Sudan, part of Uganda, most of the Belgian Congo and the northern extremity of Angola. It is a matter for wonder that, with so extensive an endemicity, there are not more outbreaks observed and that the infection has, so far as we know, never found its way through to the east coast of Africa.

A report made in 1934, giving the past incidence and distribution of yellow fever in West Africa, contains the following information:

In Nigeria, 120 localities were examined, among them many small villages, altogether 5607 specimens of blood were tested and 1508 or 27 per cent were positive, in the Gold Coast 33 localities, 861 samples, of which 168 or 20 per cent were positive, in Sierra Leone 5 localities, 149 specimens, 19 or 13 per cent positive, in the Gambia only 2 localities (one of them Georgetown which draws from small villages in the vicinity), 68 specimens, 18 or 26 per cent positive, in Liberia 3 localities, 96 specimens, 6 positive, in Dahomey 5 localities, 188 specimens, none positive, in the Niger 11 localities, 481 specimens, 104 or 22 per cent positive. Together 181 localities, 7580 specimens, 1879 or 25 per cent positive. Of course 7580 specimens are from a very small proportion of the millions of inhabitants of West Africa. [It will be noted that the addition is not correct, perhaps two localities have been omitted. As they stand the localities total 179, the specimens 7450, and the numbers positive 1823 or 24.4 per cent.]

As regards the Anglo-Egyptian Sudan other tests showed that the infection had been some six years before probably endemic in Bahr-el-Ghazal, and in Mongalla a year earlier, in the Upper Nile Province in 1916 and 1923, and in the Nuba Mountains at the beginning of the century. In the north of the Sudan no positives were obtained. While we are speaking of the Sudan it is worth noting that de Vogel gave an account of Sudanese soldiers employed at Vera Cruz during the Mexican War of 1863-7, stating that they were immune to yellow fever. This fact, together with those just given, tends to show that yellow fever must have

existed in the Sudan for a long time Viscerotomy specimens of the liver were asked for, to be sent from as many as possible of those with jaundice or dying of fever of unknown origin after an illness of eight or nine days Thirty such specimens were sent, but only one had the lesions regarded as typifying those of yellow fever ¹

In addition sera from twenty-nine subjects were sent to London and of these there were nine which gave the mouse protection test, eight from Southern Sudan and one from Wad Medani Again, we must note that from 1929-31 or even earlier cases have been seen in the Sudan presenting a peculiar syndrome of moderate fever, albuminuria, deep jaundice and vomiting, some were fatal and the livers showed marked necrosis Mouse protection tests were negative There is a strong resemblance to the disease reported by Beeuwkes, Walcott, Kumm and Hudson, seen by them in Nigeria—an "obscure infective disease associated with jaundice," the Kukuruku disease—and referred to above (p 321)

Deductions from the results of this test must be made only after due deliberation Dr Russell, when writing to the Yellow Fever Commission, stated that

veritable endemic foci of yellow fever are fewer and more circumscribed than is sometimes supposed, but the centres liable to the occurrence of epidemics of brief duration are more numerous and cover a wider geographical range It is desirable that the difference should be emphasized in order to correct the alarm caused by loose statements indicating without qualification that yellow fever is exceedingly widely distributed in West Africa

The tests have shown that Sir Rubert Boyce was wrong in his belief that the West African native "is as saturated with yellow fever as with malaria" On the contrary, they show that there are areas where the disease has never existed, others where it existed formerly, but not for a decade at least and probably longer, and, thirdly, that even in places where it is endemic all the inhabitants do not become infected

We do not, at present, know what importance we ought to

¹ Another was from a man of 25 years with a somewhat suspicious history whose liver changes were regarded by C M Findlay as highly suggestive He had arrived at Malakal after a four days' journey from Liri Nuba, sixteen days later he was seized with epigastric pain and vomiting, and in three days became intensely jaundiced and comatose and he died after six days' illness, without fever In spite of the resemblance of the liver changes to those of yellow fever, the absence of fever and the early jaundice and the onset with epigastric pain and vomiting are points against the diagnosis, the clinical history is rather that of acute yellow atrophy of the liver

attach to occasional positive results in individuals who, so far as is known, have never suffered from yellow fever, nor lived in an area where this disease occurs. For example (see also later) two positives have been found among ninety-two sera examined from natives in Southern India. Dengue is common there and is conveyed by the same vector, more tests might be carried out with sera from dengue patients at different stages of their illness, so far such sera have shown no protective power, according to the evidence of Stefanopoulo and of Beeuwkes after testing the sera of those who had been victims of the late epidemic at Athens. There may, of course, be exceptional cases of non-specific immunity.

To study the problem of yellow fever in the Gambia Protectorate samples of blood were obtained from not less than forty persons, ranging in age from under ten to over forty years, in Bakan, Brikama (near Bathurst), Kerewan (20-30 miles from Bathurst), Georgetown (60 miles from Kerewan), and Basse (35 miles from Georgetown). In all five towns between 20 and 33 per cent gave positive results to the protection test—20 per cent in Basse, 33.8 in Brikama, and, in children below the age of ten years in Bakan and Kerewan, 36 per cent, although no record could be obtained of any recognized case of yellow fever in Bakan. *Aedes ægypti* is rare, and is often not found at all, in rural areas in the Gambia, but seven of the mosquitoes found experimentally capable of transmitting infection are present, namely *Aed. luteocephalus*, *Aed. vittatus*, *Aed. simpsoni*, *Culex fatigans*, *C. thalassius*, *Eretmopodites erythrogaster*, and *Mansonia africana*. It is possible that mosquitoes other than *Aedes ægypti* may act as vectors in nature (see later, Jungle yellow fever), and also that other animals, wild or domestic, may be reservoirs of infection, monkey-blood samples were negative, but those of two sheep were positive to the protection test.

As regards East Africa, if the mouse-protection test is accepted, yellow fever exists in Uganda. Between 1903 and 1935, at the New York laboratory of the Rockefeller Foundation, 564 sera from various districts, usually 20-30 from each, have been tested and 16 have given positive results, four from the West Nile district, three from Kilgum, two each from Toro, Kigezi and Bungoro, and one each from Madi, Lango and Bugwere, indicating that yellow fever has been endemic over a wide area of Uganda in the not-far-distant past. The possible danger of spread, or introduction by aeroplanes, to fresh areas is, thus, very real. To obtain

more accurate data viscerotomes are being provided, for the findings of the protective tests caused some alarm since, although medical officers had been warned to pay special attention to cases of fever of doubtful origin or nature, no cases of yellow fever were reported

Tests have also been made with specimens of blood taken from the inhabitants of the native quarter of Zanzibar, but all were negative. If introduced the infection might set up a serious epidemic, for *Aedes larvæ* are to be found on practically all the native premises

Turning to the New World, yellow fever has had a wide distribution in South America, every part of it seems to have been attacked at one time or another, and, though it has been believed that the disease was probably present before the Guayaquil outbreak of 1750, endemicity was, it would appear, not established along the coast of Brazil until the middle of the nineteenth century, in spite of the fact that there is record of a very suspicious outbreak in 1686-94. The disease extended far inland along the Amazon where it became endemic, while along the Parana Valley brief epidemics occurred when infection was introduced through Buenos Aires. It did not, however, spread far from the coast or the banks of the larger rivers

In the early years of the present century infection was widely dispersed and, as in Havana, anti-mosquito campaigns were carried out in Rio de Janeiro, Pará, Iquitos and Panama, and the success in Havana led people to believe that eradication would be equally simple elsewhere. Between 1915 and 1919 preliminary surveys were carried out and the elimination campaign undertaken. Guayaquil, Ecuador, on the Pacific coast and a small part of North-east Brazil on the Atlantic side, were believed to be the only important centres. From 1920-4 cases of the disease were reported from Mexico, from Central America, Colombia, Peru and Brazil, but the campaigns which were organized rapidly suppressed it, at least held it in check, and hopes were entertained that the infection would soon be eradicated. Two years later, however, in 1926, non-immune troops had to traverse this focus and the inevitable outbreak occurred and spread to several States, though it did not persist. For a year no more cases were heard of, then in 1928 it reappeared again in Rio de Janeiro, after an absence of twenty years, and cases were cropping up at several points in northern Brazil, and infection spread the next year to the south. Cases of local infection were reported from the State

of São Paulo on the south to that of Pará on the north and cases were seen on board vessels at ports from Buenos Aires on the one side to Manaus, a thousand miles up the Amazon, on the other. In 1929, after an interval of six years, yellow fever appeared in Venezuela and in the interior of Colombia. In short, by 1930 the method of 'key centre control' had not succeeded in eliminating the disease from Brazil. This year marked the beginning of a new period, as already noted, characterized by the introduction of the viscerotome and the mouse-protection test for discovering otherwise unrecognized cases of the disease.

In 1931, therefore, an immunity survey of South America was started and it has covered all the Brazilian States and places in Paraguay, Bolivia, Chile, Peru, Ecuador, Colombia, Venezuela, British, French and Dutch Guianas. Wherever it was feasible a hundred samples of blood were obtained, fifty from those under, and fifty from those over 15 years of age. The results were highly instructive and interesting. No evidence was forthcoming of unrecognized outbreaks in recent years, transmitted by *Aedes*, in Chile, in Peru west of the Andes, in Ecuador, Colombia, in the coastal and Orinoco Valley regions of Venezuela, in the Guianas, in the Paraná River valley, in Paraguay, Bolivia, or the States of Matto Grosso, Goyaz, Minas Geraes, and São Paulo in Brazil. The outbreak in Colombia in 1929, however, was found to be more widespread than had been generally admitted or believed and the infection was still present in the Magdalena Valley, though the towns themselves have not been invaded of late years. Now, the *Aedes* is common in the latter, the towns, but was not found in the Magdalena Valley (the importance of this observation will be seen later).

The protection test demonstrated further that yellow fever had been much more highly endemic in the period 1925-31 in the coastal region of Brazil east of a line extending from Rio de Janeiro to the mouth of the River Amazon than reported outbreaks would have led people to believe. In places where no clinically recognized and diagnosed cases had been recorded for more than a quarter of a century immune reactions were given by 60 to 90 per cent of sera tested. Similarly, in the Amazon Valley, "the heart of America," widespread immunity was found although no case had been reported for twenty-five years or so. In other words yellow fever had continued to exist in silent form in Bolivia, Peru, Colombia, and in the Valley of the Amazon. But—and this is the important fact to note at this stage—the endemicity in the Amazon Valley could not be ascribed to repeated or continuous

dissemination from the larger centres, because the percentages of immunes in these centres were lower than those in places beyond them, and, secondly, in certain parts of the valley where yellow fever undoubtedly existed, *Aedes ægypti* could not be found

The results of the surveys carried out by the mouse-protection test in places where yellow fever was not known on clinical grounds to prevail, may be summed up briefly

In certain districts in the Anglo-Egyptian Sudan a high percentage of sera yielded positive results, reaching as high as 78 in Kau, although no evidence could be obtained to link up these results with the existence of any yellow fever or even diseases resembling it. In the Belgian Congo, of those whose sera in 1932-3 reacted negatively, 6 per cent gave a positive when re-examined two years later, in spite of the fact that no cases of clinical yellow fever had been detected in the interval. Further, after an outbreak of what was diagnosed as infective jaundice, which occurred in Libenge, near Ubangi, the percentage of positive sera rose from 6 in 1932-3 to 46 among those who had passed through an attack of this 'infective jaundice' and to 26 among others who have no history of having suffered from the disease. The fact may here be referred to that the mouse-protection test has been carried out with sera of patients convalescent or recovered from infections liable to be confused with yellow fever, such as certain forms of malaria, blackwater fever, dengue, epidemic jaundice (Weil's disease) and Rift Valley fever, but the results have been negative.

In the West Indies, in Cuba, Jamaica, Barbados, St Lucia, Trinidad and Porto Rico, no indication was obtained of any yellow fever during the past twenty years. From a study of the results obtained with sera from Mexico and Salvador, the youngest person whose serum gave protection was born in 1925, that is, was then ten years of age, though the last case reported on clinical grounds occurred in 1921 in Mexico and 1924 in Salvador.

Occasionally positive results are given to the mouse-protection test by sera taken from animals, domestic animals, birds and even reptiles. These anomalies at present have no explanation and it has been concluded that, as regards epidemiology and epizootology, animal sera results, except in the case of monkeys, are to be disregarded.

Facts such as the foregoing—the mystery of positive protective sera among inhabitants of regions where yellow fever has not

within a considerable number of years been diagnosed clinically, and still more puzzling where the disease has never been known to occur at all—further study, it is hoped, will elucidate

We are now in a position to see that the mouse-protection test has been and continues to be of the highest value in confirming or annulling the diagnosis of yellow fever in suspicious cases, but in that it has given evidence of the disease in places where it was neither known nor even suspected to prevail, another problem is put before us for solution. It has elucidated obscure outbreaks of the past, as, for example, those of Santa Cruz de la Sierra, Bolivia, in 1867 and 1887 in the light of the findings of another occurring there in 1932. In 1867 the district of Abapo was smitten by a disease in which some of the victims showed the symptoms of black vomit and which was diagnosed by Dr. Sanchez, a priest there, as yellow fever. Twenty years later the same and adjoining districts were again attacked and again the diagnosis made by members of the Catholic Mission there was yellow fever, but they thought that this diagnosis would be neither accepted, nor even acceptable, and correctly so, for the report was not again referred to until 1932. Soper, quoting from the report of Ortiz, Nicolás and Cano Montobbio, translates

Without doubt many authorities will be unwilling to admit the presence of yellow fever in the heart of Bolivia, far from the places in which yellow fever generally exists and without known routes of penetration from without

There was, at first, some reluctance to accept the outbreak of 1932, in the same place and with the same symptoms, as yellow fever, because the population was small, under 20,000, and the town was more or less isolated, and at least a thousand kilometres from any focus where yellow fever had been seen for twenty years. But the evidence based on more recent methods was irrefutable and the diagnosis of the outbreaks of half a century and more was retrospectively confirmed. The same applies to the outbreak at Muzo, Colombia, in 1907.

PRESENT GEOGRAPHICAL DISTRIBUTION OF THE DISEASE AS SHOWN BY IMMUNITY TESTS

The latest reliable records of prevalence which we have been able to obtain show that the disease is still widespread, geographically. In 1935 cases were recorded from Brazil, Bolivia and Colombia in South America, and in the first deaths were numerous and both urban and rural types occurred. Records also came

from the French Congo, Dahomey, the Ivory Coast, the Niger Territory, Togo, Gambia, Gold Coast and Sierra Leone, and in the Gambia some cases also probably of the rural type, *Aedes ægypti* being absent. In Africa, however, the cases were sporadic, not numerous or epidemic in distribution.

In the League of Nations Epidemiological Report of that year, 1935, there was reproduced a series of maps illustrating the distribution of yellow fever and its vectors, together with the

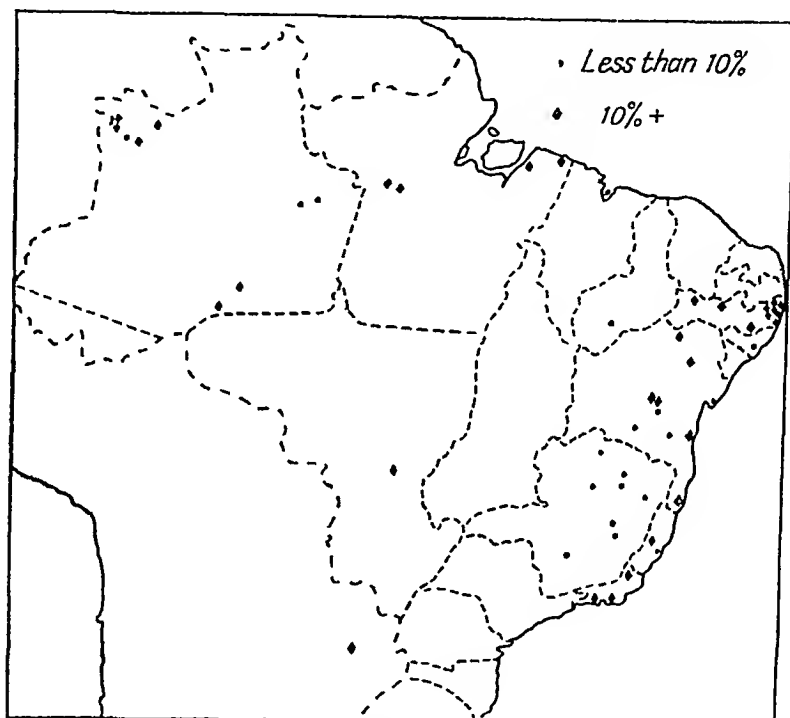


FIG 2

Results of sero-protection tests in S America, 1935

From the League of Nations report, by kind permission

epidemiological diagnostic protection tests and viscerotomy revelations. The present world distribution is given and that of the reservoirs and vectors, and the possibilities, natural and artificial, of its spread and the methods of control where it exists in endemic or endemo-sporadic form are pointed out.

Next, we may summarize the results of a four years' investigation (from 1931-5) undertaken to determine the geographical distribution of immunity to yellow fever in man. The mouse-protection test was used, sera being sent from Africa and South America to New York in sealed ampoules kept on ice in transit. This survey was the outcome of the recommendations of the

Ninth Pan-American Sanitary Conference (1934) regarding the disease These were

1 Systematic investigation of the distribution of immunity to yellow fever among the inhabitants of all tropical countries and other parts to establish the distribution of the disease in recent years

2 Systematic histo-pathological investigations of specimens obtained with viscerotome from all dying of febrile disease after an illness of ten days or less



FIG 3

Positive viscerotomy results in S America, 1935, showing confirmation of distribution as revealed by sero-protection tests (see Fig 2)

From the League of Nations report, by kind permission

3 Antilarval services to be organized, of a permanent nature

4 Three-monthly reports concerning the organization of antilarval campaign and Aedes indices

5 Determination of supplementary methods in rural regions where antilarval methods may be ineffectual or impracticable

6 Preventive vaccination of susceptibles travelling into or through endemic regions and of rural populations where yellow fever is known to exist

7 Founding of special laboratories for examination of viscerotome tissue, for carrying out the mouse-protection test, etc

Special study of Aedes in Africa was called for, especially in the interior, and intensive studies to determine more accurately

the limits of endemicity and the factors which limit this endemicity

As regards Africa it was found that immunity is widely, though irregularly, distributed from the coast of Senegal for 3300 miles or so to the upper reaches of the White Nile in the Anglo-Egyptian Sudan, bounded on the north by the Sahara, and on the south by a line along the north of Angola running east to the southern part of the Belgian Congo. The western part of this, extending to Nigeria, has experienced several epidemics, both on the coast and inland, and is still having them—in fact, nearly all the historic outbreaks in Africa have occurred in this area. The eastern part has never been regarded as a yellow-fever area and many sera, tested because the subjects gave histories of yellow-fever attacks, proved negative, and the heavily immunized areas seemed to be continuously endemic rather than epidemic, unless the virus be of a strain different from the classic. In this area there exists a zone of high prevalence of immunity among children and adults.

The survey of South America was on similar lines and included all the Brazilian States and Paraguay, Bolivia, Peru, Ecuador, Colombia, Venezuela and the Guianas. There was no evidence of recent outbreaks which had been missed in these places, but it was found that infection was persisting in certain districts of the Magdalena Valley where *Aedes ægypti* is not found, while the river towns, in spite of a high *Aedes* index, have not been affected in recent years. The disease has continued to be endemic in Bolivia, Peru, Colombia and the Amazon regions of Brazil, 'silent regions,' but since the percentage of immunes in the large centres of population in the Amazon Valley among the lower age groups is less than that outside them, this persistence of endemicity is clearly not due to continued introduction of the virus from the larger centres. Also, the disease is endemic in certain parts of the Amazon Valley where careful search has failed to find *Aedes ægypti*.

8 YELLOW FEVER WITHOUT *ÆDES ÆGYPTI*

We come now to a consideration, from the historical aspect, of yellow fever in the absence of the usual vector, *Aedes ægypti*.

This was first observed in Valle do Chanaan, Espírito Santo, Brazil, in March 1932. Evidence therefore included observation of the clinical course, the findings at autopsy, the positive results of the protection test with serum of recovered patients, and of the inoculation of susceptible animals. Those attacked were

adults working in the woods, children who accompanied them or visited them to bring them food. Those who stayed in the dwellings away from the forest were not attacked. As the outbreak died down after attacking a relatively small proportion of the inhabitants it was thought that the virus had perhaps been introduced from near-by towns where *Aedes* was abundant, but finding conditions for promulgation unsuitable had come fortunately to a premature end.

Soon afterwards, a small Indian village in the forest in the lowlands of Bolivia, named San Ramón, was the site of an outbreak. Here, again, no *Aedes ægypti* was found but infection was conveyed thence to Santa Cruz de la Sierra (see above, p. 419), where *Aedes* was plentiful. Here the usual anti-mosquito measures soon brought the outbreak to an end.

The succeeding year, 1933, confirmation was obtained of the existence of infection in the absence of *Aedes* in two other localities, namely Lauro Sodre, Amazon Valley, Brazil, and Caparrapi in the Magdalena Valley, Colombia. In the latter there were twelve deaths among thirty-seven cases, all of them workmen in the woods. By 1934 interest in the so-called Jungle or Rural Yellow Fever was increasing, while for a time, at least, the usual mosquito-borne disease took second place, for, though a single case was reported far up the Amazon and a few in north-east Brazil, all proved by viscerotomy specimens, outbreaks of the jungle type occurred in Magdalena and Orinoco Valleys of Colombia and in three widely separated places in Brazil, in the States of Pará, Bahia and Matto Grosso. Some writers mention 'silent areas' of endemicity, but this is not a good term, fatalities occur in these areas as in urban districts, but the former are more likely to pass unrecognized.

During the three years, 1934-6, many observations of importance were made with regard to this type of yellow fever. In 1934 and 1935 an outbreak occurred at Coronel Ponce on the Planalto of Matto Grosso, Brazil, and an account of it and investigations connected therewith have been published by A. W. Burke in 1937. Without going into too minute detail we may say that 201 persons were attacked, the diagnosis being established, as at Valle do Chanaan, by the clinical course, the post-mortem findings, the results of the protection test, and infection of white mice by the human virus. The nearest towns where *Aedes* abounded had a population among whom, especially the children, the immunity rate of yellow fever was low, hence the probability was altogether against the infection having been introduced from them. At a

Government post in an isolated spot known as Simões Lopes, a hundred miles north of Coronel Ponce, the Indians showed a high percentage of immunes, both children and adults, it was more probable, therefore, that the infection had come from this jungle district of the Amazon Valley. Five wild monkeys, *Cebus*, were captured in the district and all were shown by the mouse protection test to be immune, they, therefore, and not man alone, were also natural reservoirs of infection. Further examination of human sera from those living close to and working in the jungle and those in the villages more remote showed that the immunity rates increased from without inwards, being highest in those nearest the jungle.

Muzo in Colombia is another region where yellow fever remains endemic though *Aedes ægypti* is absent. In 1907 the disease was reported there, care being taken to distinguish it from malaria and relapsing fever. Labourers are constantly arriving from other parts of Colombia to work in the emerald mines and though the district is not densely populated cases of yellow fever constantly occur. *Aedes* was said to be present in Muzo in 1907 (a few years after the mosquito transmission was proved), but this has never been confirmed and is now believed to have been recorded in error. Gorgas reported in 1917, having visited the district the year before and being as well acquainted as anyone with the clinical features of the disease, that the suspected patients whom he saw could not be suffering from yellow fever "since the conditions necessary for endemicity did not exist". Examinations of tissue taken by viscerotomy during 1934-6 showed that the disease was endemic over a wide area sparsely populated between the right bank of the Magdalena River and the mountains east of it, but that, so far as was known, only those close to or working in the forest were attacked. The endemicity of Muzo seems to have been constant for at least thirty years, though *Aedes* is absent.

There is no need to multiply examples, but one more is too important to pass over, namely, that known as the Goyaz outbreak of 1935-6. It involved not only the southern part of Goyaz, but the west and south-west of Minas Geraes, northern Paraná, southern Matto Grosso and a large part of São Paulo State. The area is several hundred thousand square miles and is sparsely populated, from most of it yellow fever had never been reported and certainly none for more than twenty-five years, but during this outbreak there must have been hundreds, nay thousands, of cases, but practically limited to places where *Aedes* could not be found. Hundreds of deaths occurred in an area of about 100,000

square miles and since yellow fever had never before been known to occur there this outbreak came as a most unwelcome surprise

There is no certainty that jungle yellow fever is limited to the New World. In 1935 a Colobus monkey caught in the Goaso district of Ashanti was proved to be immune. Again, in the Gambia Protectorate, except in Bathurst where the usual mosquito-transmitted, urban type occurs, the disease though endemic does not appear in explosive outbreaks, and the infection is not mosquito-borne, it is contracted in the field, not in the houses, and families are not attacked as with the ordinary type, and here also, as in the Gold Coast, the blood of monkeys in the endemic areas is found to contain immune bodies—in other words, there is no little similarity between yellow fever in parts of the Gambia Protectorate and the jungle form of South America. If this is a fact, the epidemiology of yellow fever in Africa, as in America, becomes a far more complicated problem than has hitherto been supposed, because the severing of the man-*Aedes*-man chain will not bring about its eradication, and all that can be done with our present knowledge to procure personal prophylaxis is to take advantage of methods of artificial immunization.

Jungle yellow fever then may be defined as "Yellow Fever occurring in rural, jungle, and fluvial zones in the absence of *Aedes ægypti*." The differences from the urban, mosquito-transmitted type may be seen set out in the table on page 426.

As Dr F. L. Soper, of the Rockefeller Foundation, has said, at present it must be confessed our knowledge of jungle yellow fever is scanty and what we do know raises more problems than it solves. One or two of these may be mentioned.

- 1 Formerly, a dense population, a seaboard town and abundant *Aedes* were considered essential, what then enables jungle yellow fever to continue in the absence of each and all of these?

As a preliminary to determining this search will have to be made for possible vertebrate hosts and reservoir hosts and invertebrate vectors other than *Aedes ægypti*. On an analogy of rats and plague it may be a natural disease in monkeys and accidental in man. Up to the present the disease has been observed only in those districts where forest-clearing is in progress and where monkeys exist, although the sera of these monkeys show immunity, other hosts cannot as yet be excluded.

- 2 Secondly, why do we not more often see outbreaks of the usual *Aedes*-transmitted type in towns started by cases of the jungle type ?

This is more readily answered. The two types have been shown by immunity and other tests to be due to the same virus essentially, and the jungle type can be transmitted by *Aedes* and, moreover, as seen in Socorro, Colombia, in 1929, the jungle type can originate an urban outbreak. One obvious reason for the rarity of this is that a yellow-fever patient is infective during

	Urban type	Jungle type
Locality	Contracted in the house or near by	Contracted in the field, especially in areas where forest clearing is incomplete
Vector	<i>Aedes ægypti</i> , a domestic mosquito	Not certain, <i>Aedes ægypti</i> absent
Time of Day	More at night	In daylight, while at work
Age and Immunity	High rate in the young, in some places 50 per cent at ages 1-4 years, 82 per cent at 40 years or over	Generally low and mostly in adults. Nil under 4 years, 38 per cent at 40 years or over, if working in jungle
Sex	Male and female equally	Males more than females, because men go to work in the forest while the women stay at home
Sequence	Man-mosquito-man	Not known. May be of the nature of an accident in the course of an epizootic (like plague)

the first seventy-two hours or so only of his attack and by the time he is brought to a town for treatment or observation he is beyond this stage

- 3 Thirdly, what methods of control can we employ to combat jungle yellow fever ?

If monkeys prove to be the sole vertebrate reservoir host, their reduction would benefit, as was suggested in the case of trypanosomiasis destruction of big game reservoir hosts, but this entails no slight risk as the virus may adapt itself to another, or the vector be more ready to attack man when deprived of its natural host. Elimination of the invertebrate vector is theoretically sound, but open to two strong objections, one that the vector is



FIG 4
 Places in South America in which jungle yellow fever has been observed from
 March 1932 to October 1935
 Reproduced by kind permission of Dr F L. Soper

not at present known,¹ and the other that destruction or elimination of an insect vector in a jungle is, on the face of it, an impossibility. We are left, therefore, with the employment of artificial immunization, the best and, at present, the only feasible method.

In connection with the question of vaccination as a protection against jungle yellow fever, Soper's view is that all at risk should be vaccinated, even infants and pregnant women.

Some have believed that there might be a possibility of the vaccine being taken up by the vector and thereby acquiring increased virulence, but the general conclusion is that this does

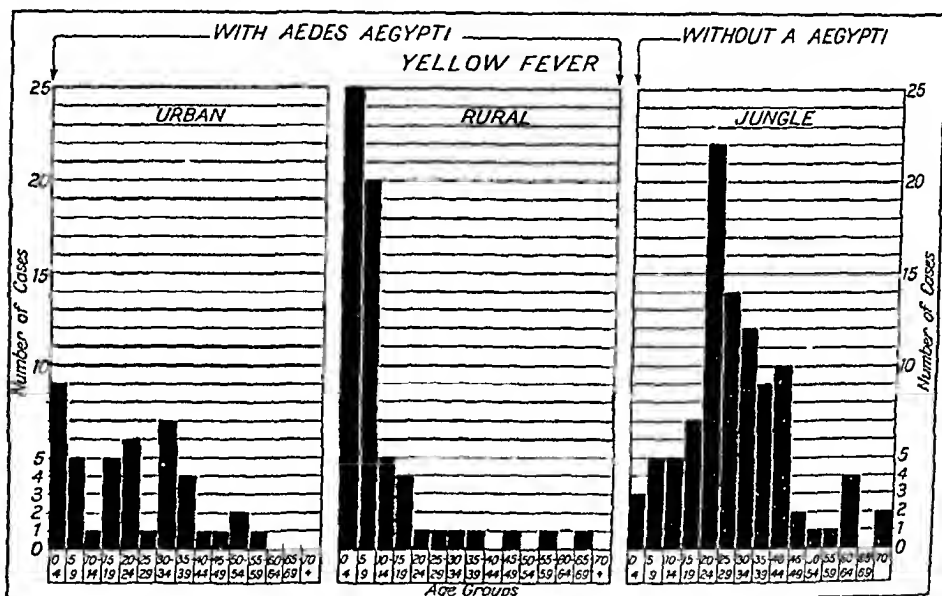


FIG 5

Age distribution of cases of yellow fever confirmed by liver changes, from 1930 to Sept 1935, in Brazil, Colombia and Bolivia

Reproduced by kind permission of Dr F L Soper

not occur. The average duration of post-vaccinal immunity is not yet decided, it is certainly one year and may be as much as two, but the need for re-vaccination should be controlled by serum

¹ Recently (July 1938) another species of *Aedes*, *Aed serratus*, has been proved to be a natural vector in jungle (rural) areas where monkeys are found infected in nature. R C Shannon, Loring Whitman and Mario Franca seized the opportunity of an outbreak of jungle yellow fever in Rio de Janeiro in 1938 to collect 24,304 mosquitoes on the spot. Among the many species captured two gave evidence of being natural vectors, namely *Aedes leucocelænus* and *Hæmagogus capricornis* since their bite proved infective, *Aedes serratus* was among those caught, but their specimens proved negative. One or more species of *Sabethinae* may harbour the virus, but natural transmission by them was not proved, they conveyed the infection only by injection.

protection tests It is further to be borne in mind that a negative protection test after vaccination does not necessarily imply that the subject has again become highly susceptible, there may be some degree of tissue immunity still remaining

9 RECAPITULATION ADDITIONAL REMARKS

In the foregoing pages we have considered in some detail the investigations and research that have been made on the subject of yellow fever—its transmission, the virus, its characters, its control, and so forth—since the beginning of this century We trust it will not be regarded as vain repetition and waste of time if we gather up the threads, as it were, and recapitulate the main features which have historical interest

Sellards has stated that the activities in the study of yellow fever fall naturally into three periods First, that prior to 1900 when transmission by the vector, *Aedes aegypti*, was proved Concerning this sufficient has been said and we shall not refer to it again here Second, the succeeding twenty-eight years, during which any experiments carried out involved the consent of human volunteers Throughout this period the chief work was application of the findings of the United States Commission of 1900 Third, from 1928 to the present day, during which advance has been very rapid, thanks largely to the staff of the International Health Division of the Rockefeller Foundation and to those working in association with them—to Adrian Stokes who, with Bauer and Hudson in 1927, found that the monkey, *M sinicus*, and, later, *M rhesus*, was susceptible and thus was a serviceable animal for laboratory study, to the establishment of the Asibi strain from Senegal in several laboratories in London, Europe, New York and Boston, so that results obtained in different parts of the globe could be compared and tested, to Theiler who developed the mouse infection and so facilitated and lessened the cost of research and thereby opened the way for extensive researches

Prior to 1930 and the employment of protection tests to establish a diagnosis retrospectively there were only clinical grounds to go upon and it was a well-known fact that at the beginning of an epidemic—the important time if an outbreak was to be checked—typical or well-marked cases are uncommon and that often the milder forms predominate 'Malaria' was the label on the medical dustbin into which all doubtful and most difficult cases were cast, moreover, true malaria may, and often did, exist in

the same localities as yellow fever. As we have seen, Chisholm believed yellow fever to be typhus modified by a hot climate. Other diagnoses, which by staving off the true might lead to loss of valuable time in prevention, were influenza, especially the gastric form, as actually occurred in Barbados in 1909, Weil's disease (as in Brazil with Noguchi's first studies), dengue (as in St Thomas and other West Indian Islands in 1827), blackwater fever (though confusion with this should not arise, since the urine contains hæmoglobin or methæmoglobin and not blood, vomiting occurs, but Faget's sign is absent, and so forth). Lastly, in children yellow fever may run a very anomalous course when compared with that in adults and consequently may pass, often has passed, unrecognized. An instance of this is the Belsize outbreak in 1905, of which Sodré and Conto wrote

During an epidemic of yellow fever, if a child is affected by a fever lasting more than 24 hours and followed by symptoms of nervous agitation, the diagnosis in 95 per cent of cases will be [² should be] yellow fever

All this uncertainty could be set at rest by the application of the knowledge, first that the blood of a patient is infectious in the first three days of fever, and second, that the blood can, by our utilizing low temperatures, be preserved while retaining its infectivity and so be sent to a laboratory at a distance in order that, thirdly, monkeys which have been found susceptible may be inoculated and used as a test for protective properties or the absence of them in the serum in question. The application of the uses of the virus in mice by Max Theiler, two years later, the outcome of which was the 'mouse-protection test,' still more facilitated the diagnosis of doubtful cases and later led to its uses for retrospective diagnosis in epidemiological studies, by Beeuwkes and Mahaffy in Africa, Siler and Bates in Central America and Panama, all positive, in China (negative), British India (negative) and other places. From results so obtained, Dr F. E. Russell, Director of the International Health Division of the Rockefeller Foundation, concluded that

veritable endemic foci of yellow fever are fewer and more circumscribed than is sometimes supposed, but that the centres liable to the occurrence of epidemics of brief duration are more numerous and cover a wider geographical range. It is desirable that the difference should be emphasized in order to correct the alarm caused by loose statements indicating without qualification that yellow fever is exceedingly widely distributed in West Africa.

Another innovation which has assisted diagnosis and epidemiological investigation was the introduction of the viscerotome for

taking portions of liver tissue, when complete post-mortem examination is refused. By 1935 more than 65,000 such specimens had been taken in 1500 different places. The instrument was *not* introduced, as is often thought and sometimes stated, in order to aid health officers in coming to a diagnosis, for suspected cases ending in death should be subjected to autopsy. The purpose, the initial purpose, of its introduction was the discovery of fatal cases in otherwise 'silent areas' and it is used as a routine method on all persons over one year of age dying within ten days of the onset of a febrile illness. Its use has resulted in the discovery of unrecognized yellow fever in natives and in foreigners, in adults and in children, in urban and rural areas, within and without regions of known endemicity. If examination of the tissue gives positive information, we know that at a certain place, on a certain date, a certain person died of yellow fever; if a succession of specimens gives negative findings we are fairly safe in concluding that yellow fever is no longer endemic in that area.

In 1929 the Rockefeller Foundation formed a co-operative service with the Federal Service in Rio de Janeiro and drew up the following regulations

- 1 Members should have the right of entry to all premises
- 2 No unauthorized person could enter any closed building until it had been inspected by a member of the Service
- 3 Larvicide was to be applied to all deposits where mosquitoes were found breeding. Special squads were appointed to search for foci where *Aedes* was breeding, to apply oil as a routine to all water-containers found with larvæ. To other squads was assigned the duty of capturing adult *Aedes ægypti*. Since a week elapses between oviposition and the pupal stage, weekly visits were the rule to forestall the development of mosquito-producing foci
- 4 Responsibility for domestic breeding sites rests on the occupier, or the owner, the existence of such sites was made penal
- 5 Autopsies and the taking of specimens by viscerotome were authorized, and burial before the representative of the viscerotome Service had given his visé was prohibited
- 6 Anyone opposing the work of the Yellow Fever Service was liable to fine and imprisonment

Let us briefly review the results of this co-operation. It was believed that the country was almost free from the scourge, but almost at once the disease was found to be present in the State of Rio de Janeiro in the south, the State of Pará at the mouth of the Amazon, and of Pernambuco in the north-east. This last State is a long, narrow territory divided (by Soper) into four epidemiological zones. 1 Recife, an endemic key-centre, with a population of 250,000 or more, where the disease would persist

until stringent anti-Aedes measures were enforced 2 Coastal plain where the virus persisted and showed its presence when non-immunes entered—a regional endemic zone 3 Behind the last, a well-peopled zone where epidemics among the natives were frequent—an endemo-epidemic zone 4 The hinterland, the western part of the State, sparsely populated and with no history of past infection

In June 1930 a scheme was drawn up organizing anti-mosquito measures for all towns of 2000 population or more in the first three of these zones The viscerotome (see Regulation 5 above) was made use of and revealed a peculiar, in fact a startling condition of affairs, namely, absence of the disease from the capital city, Recife, but its presence in the other three zones (*i e* including the hinterland, or what had been designated the non-infectable zone) This meant that the constant and energetic application of measures in the key-centre had resulted in elimination from the centre only

More energetic application of the same measures to the smaller towns and finally even to villages with only fifty houses or even fewer resulted in clearing out infection from all but the hinterland, the end desired was not attained here until every house in the rural district was included, showing that with the Aedes-transmitted form of the disease antimosquito measures, if intensified, can be made efficacious even in rural areas

It will be remembered and must constantly be borne in mind that Aedes differs from Anopheles and other mosquitoes in being essentially a domestic insect, preferring artificial containers to pools The presence of street puddles, ponds and marsh, absence of proper drainage and sewage disposal in a town, have all been incriminated as favouring the breeding of Aedes and so of producing yellow fever, but the clearing up of these conditions does not affect the breeding of this mosquito, better than all (from the yellow fever point of view) is the installation of a piped water-supply to do away with domestic storage in receptacles Crab holes collect water and these too have been incriminated, but in these another striped mosquito breeds—*Democerites canerosum*—and has possibly been mistaken for *Aedes aegypti* Examples of disappearance of the disease after installation of a piped supply are many, mere mention of one or two will suffice, Philadelphia, Baltimore, Norfolk (Virginia) where in the early nineteenth century fire-barrels and other containers on the wharves bred the mosquitoes in abundance If infection be introduced into a susceptible community where Aedes abounds, it will spread slowly at

first because of the incubation periods, first in the mosquito, and second in the persons bitten by the latter, but each such person becomes a centre from which secondary (or rather tertiary) cases arise and the subsequent extension will be rapid. If, however, infection and *Aedes* are introduced at the same time, these secondary foci will not be established and the spread can only be according to the rate of breeding of *Aedes* and extension will be slow, as exemplified at Boston in 1798 (q v). So also in the Swansea outbreak of 1865, infection was brought with *Aedes* on board the *Hecla* from Cuba, the infected insects leaving the ship and finding victims on shore, but no secondary cases were seen.

As in the case of *Anopheles* and malaria, it would seem that there must be a 'critical number' of *Aedes* present, and this will vary in different parts of a town, for instance many in sparsely populated quarters where there are immune natives and few in European hotels where the non-immune congregate. An analogous condition is seen in the case of rat fleas and plague, the disease breaking out when the rat-flea index rises to three or over.

In brief, for *Aedes* to continue in a temperate climate or one with definite winter and summer two things are necessary. The low temperature of winter must not be sufficient to destroy the hibernating eggs and the summer temperature must be high enough for their development. Thus, in the eastern Rockies and the southern Andean Cordilleras the first is the ruling factor, in the higher parts of the American tropics the second. So, in the Memphis outbreak of 1897 the seasonal fall in temperature was sufficient to suspend the activity of the mosquitoes and a lull occurred in the return of cases and if the interval be long enough for patients to pass the infective stage, the outbreak will end unless infection is again introduced. At the other extreme, doubt has been thrown on the possibility of yellow fever being able to occur in Mesopotamia or on the shores of the Red Sea, because the summer temperature (109–110° F) is above the thermal death-point of *Aedes*, according to experimental work. This, however, is an argument of little weight, the insect might find cooler spots or oviposit in cool, porous water jars. On the other hand, *Aedes* may live, but does not convey infection at temperatures below 68° F and probably a higher degree (the optimum is 80–87°) is needed for the virus to develop, if so the *tierra fria* of Mexico is uninfectable.

As we have said on more than one occasion, for existence and spread of the disease, three things are necessary. Infection must be present, there must be initial cases, infectable mosquitoes and

non-immune persons. Failing any of these the disease cannot exist or at all events persist. (We are not including jungle yellow fever.) Areas are said to be "temporarily epidemic" when infective mosquitoes are present and the supply of susceptibles is maintained by constant immigration, as at Rio de Janeiro, Havana, Guayaquil.

Thus the disease has disappeared, as it were spontaneously, from Cartagena, Barranquilla, Maracaibo, Circuta, Haiti and San Domingo, Porto Rico, St Thomas and elsewhere, without any special anti-mosquito measures being put into force, and though *Aedes* still abounds. Where travelling is easy, as in Yucatán and Campeche, and *Aedes* numerous in the sisal haciendas, unless sanitary measures are enforced the infection remains endemic, it is well in such places to press anti-mosquito measures in the intervals when, from lack of susceptibles, yellow fever is at a low ebb.

Again, though no work has been carried out directed towards abating the prevalence of yellow fever in the southern Caribbean and the Lesser Antilles, the disease seems to have quite disappeared since the Great War, aided by the work of sanitation carried out at Coro, Venezuela, in 1917-18, but mainly because there has been no fresh introduction of infection from Vera Cruz, Havana, Panama and other places whence the virus was wont to be introduced.

It has been repeatedly proved—at Havana in 1900, at Rio and Santos in 1903, Panama in 1904, New Orleans, 1905, and elsewhere—and may be taken as factual that the ordinary urban yellow fever can be controlled and even eliminated if action is taken on the lines that the source is human cases within the first three days of the attack, that the agent of transmission is the *Aedes ægypti*, a domestic mosquito which stays in or close to the dwelling where it has fed, and that this must survive for twelve days after an infective feed before itself becoming capable of transmitting the infection by its bite, and that the incubation period in the newly bitten subject is not more than six days.

When we came to feel secure in this repeated confirmation of knowledge, acquired hardly and after much study, the rural type, and jungle yellow fever began to declare themselves and upset our fond delusions.

Moreover, even if we find the vector and the mode of transmission of this type of yellow fever we cannot be certain that we shall be able to deal with it and, pessimistic though it sounds, we cannot be certain, even if we accomplish this, that Nature

will not find some other way to circumvent our efforts—the days of simple epidemiology and complacent omniscience are gone

In modern times, with the possibility of rapid travel by air, ease of transport and the ability of infected persons to be brought to a country of non-immunes, and of *Aedes* to survive and remain infective, precautionary measures are called for and should be put in force before the airship departs from places where the disease exists, measures taken at the port of arrival, though not to be overlooked, are a secondary consideration. Before departure, crews and passengers must have been free from any risk of infection for the preceding six days and the vessel itself and cargo should be rendered as free as possible from the risk of carrying mosquitoes. As a matter of fact, the real risk in practice is the chance carrying of a human case in the incubation period. Since, as the United States Public Health Service has proved, *Aedes* can be carried long distances by aircraft, measures must be taken in hand to destroy them, as by HCN fumigation, by discoids (impregnated paper disc), by Zyklon (impregnated Fullers' earth) or the gas itself, $\frac{1}{2}$ oz per thousand cubic feet. A serviceable pyrethrum preparation is the spraying fluid known as 'Pyrocide 40'. It is not a difficult matter to keep aerodromes free from *Aedes*. For those travelling from a clear port to a yellow-fever district, at present no safer method is known than immunization of the personnel and passengers.

At Singapore a Quarantine Commission for Aerial Navigation was set up in 1935, by whose orders measures of isolation before embarkation of persons suspected of having been exposed to infection are included and are in force at Juba, Malakal, Khartoum and Cairo, also systematic freeing of aircraft from insects. Further, when necessary, the aircraft and crew will be changed, and those from an endemic focus will not themselves proceed to areas where there is a risk of introducing the infection afresh. Finally, the aerodrome at the place of departure, if a yellow-fever centre, must be of the anti-amaryl type.

An International Sanitary Convention for Aerial Navigation gives countries of arrival power to repeat the procedures of inspection and disinsectization of aircraft, and examination of passengers and isolation of them, if deemed necessary. The Government of India are considering transforming the Karachi aerodrome into one of the anti-amaryl type. In 1936, at the request of the Government of India, an *Aedes* survey was undertaken at Calcutta where it plays no small part, for during the monsoon period it becomes a great nuisance, and is responsible

at intervals for outbreaks of dengue This survey showed that 12.6 per cent of the houses were infested with *Aedes*, *Aed ægypti* in particular, but also *Aed albopictus* to a small extent Dengue is common each year during the rains and in some years 30–40 per cent of the population suffers It is clear that with so many *Aedes* there is no little potential danger if yellow fever were once introduced, and with the modern facilities for speedy transit by air this possibility is not negligible More than four-fifths of the breeding-places were water-storage cisterns and collecting vessels, hence the need for continuous piped supply and frequent house inspection

In September 1936, the Government of India made an Order that no aircraft should be allowed to enter British India within nine days of leaving a region where yellow fever exists or where protection tests show that it has existed [within the lives of the present inhabitants] This rule does not apply to aircraft which has obtained a certificate of disinsectization from the Director of the Egyptian Maritime, Sanitary and Quarantine Board Experimentally, it has been demonstrated that *Aedes* placed in cages and handed in at Karachi were alive on arrival at Amsterdam and some were still alive when examined on the return voyage, at Cairo, Baghdad and even Karachi But, in actual practice, of 106 aircraft arriving at Karachi from Egypt, Damas and the Far East, mosquitoes were found in one only

The International Convention for Aerial Navigation has laid down certain regulations for disinsectization by sanitary authorities of countries traversed by aeroplanes, but forced landings might occur at places where there was no sanitary organization and mosquitoes could enter there This risk is overcome by a method ensuring disinfection during flight and an experiment was recently (in June 1938) carried out with an apparatus devised by Dr Park Ross, Deputy Chief Health Officer for the Union of South Africa, and Mr Larmuth of the South African Fumigation Company Jets of insecticide spray of *Deskito*—a pyrethrum compound in water—propelled by the pressure of a nebulizer were tested The preparation is non-inflammable, non-corrosive and non-staining, and passengers did not object to it In the actual test twelve boxes of mosquitoes were distributed in various parts of the craft, the apparatus was set working in the rear cabin and after ten minutes was moved forward to the next, and so on in succession Of 600 mosquitoes liberated all but two were killed in fifteen minutes or less

An even handier method is a development of this whereby the

insecticide is carried compressed in a sparklet bulb and is sufficient to disinfect a thousand cubic feet. The apparatus is very light, weighing only a few ounces—an important consideration in aeroplane travel.

The Pan-American Airways has instituted the following control measures to take effect from the 21st April, 1937

(1) All flying personnel not already vaccinated against yellow fever will be vaccinated in Rio de Janeiro at the Rockefeller Laboratory. This will be begun at once and will be finished as soon as possible. The personnel included aviators, radio-operators, flying mechanics, pursers, stewards, etc.

(2) Beginning May 1st, 1937, cards will be filled out for all passengers to show where they have been or have resided for the six days prior to embarkation *en route* to the United States. These cards will be attached to the passenger list of the airplane and will be available to the Quarantine Officer on arrival at destination.

To bring this part of the subject up to date we place before readers the latest available returns dealing with distribution of the disease.

In the Sudan report for 1936 mention is made of sixteen deaths occurring after a few days' fever of obscure origin. None of these was actually suggestive of yellow fever, but it was thought advisable that protection tests should be carried out with sera from persons in the Eliri district of the Nuba Mountains. Samples were collected and sent to Dr G. M. Findlay in London who examined them and reported as follows: Of thirty-nine sera from Gulfan eight (21 per cent) were positive, of thirty-eight from Kau thirty were positive (79 per cent), of thirty-one from Heiban three (10 per cent), of twenty-seven from Eliri twelve (44 per cent), of eighteen from Lafufa five (28 per cent) and of five from Nyaro three gave protection.

From these figures we must infer that the disease has been fairly widespread throughout the Nuba Mountains during recent—the past twenty—years, for the youngest positive was twelve years old. There have, however, been no cases diagnosed clinically and the infection has been entirely subclinical, at Kau, for example, where thirty were positive out of thirty-eight tested, there had been no history of any disease associated with jaundice or other symptoms suggestive of yellow fever. Noteworthy also is the striking difference in the percentages positive in adjacent and apparently similar districts, also the fact that sera taken from animals in the Nuba Mountains and seven others from the southern area were positive for the Rift Valley fever virus, although

there was no history obtained of any epizootic resembling this disease among the domestic animals of the country and it is most unlikely that they had visited Lake Naivasha in Kenya where alone, till then, Rift Valley fever was known to occur

Findings analogous to those in the Nuba Mountain district were noted by Stefanopoulo in the natives of French Equatorial Africa in the latter half of 1935. No case of yellow fever had been notified among the white inhabitants, nevertheless in the Middle Congo as many as 46.1 per cent of sera from natives, and in one department of Lake Chad region 55 per cent reacted to the mouse protection test, and some sera were from quite young children

In 1937 Findlay and MacCallum examined the sera of sixty-seven wild African monkeys from areas where human sera yielded positive findings. Of the total, nineteen belonging to six species—*Cercopithecus* from Liberia, *C. aethiops centralis* from the Anglo-Egyptian Sudan and Uganda, *Colobus vellerosus* from Sierra Leone and the Gold Coast, *Procolobus badius badius*, *P. badius waldroni* and *Cercopithecus diana diana* from the Gold Coast—were positive. These, added to previous results, give a total of twenty-two positive out of ninety-two monkeys examined. Seeing that *Aedes aegypti* is largely a domestic mosquito, it would seem that under natural conditions other mosquitoes may, even must, be potential vectors of the virus.

Actual cases of human yellow fever notified during the first nine months of 1937 were

Brazil 180 cases, 161 deaths. São Paulo 74 cases (74 deaths), Minas Geraes 62 cases (62), Matto Grosso 32 cases (13), Pará 7 cases (7), Paraná 2 (2), Acre Territory 2 (2) and Pianhy 1 (1).

Peru Perené River region 33 (13)

Colombia 29 cases, 25 deaths. Boyaca 13 (9), Santander 8 (8), Meta 4 (4), Cundinamarca 4 (4). The disease was also present in the north-west forest area of Paraguay, but the number of cases was not known.

During the same period 61 cases, 52 deaths, were reported from the Gold Coast, 14 at Accra all fatal, in Nigeria 16 (9), in French Equatorial Africa 6 (4), in French West Africa 23 (19), namely, in Senegal 14 (13), Ivory Coast 7 (4), and Dahomey 2 (2).

At Accra there were nine cases in January and February when the house-Aedes index was very low, under 1 per cent. Search revealed a disused well, hidden by overgrowth and rubbish, ten yards from the house in which the first case occurred and in the

water of this were larval *Aedes* and in the air above many adults. After this well had been dealt with no more cases occurred.

Sawyer, Bauer and Whitman reported in 1937 the results of tests made with human sera from various parts of the world. These are of sufficient interest to merit brief mention. Of 876 from Asia and Australia, where yellow fever has never been known, two gave protection, of 481 from Italy, Spain, Portugal, Canada and the United States of America, where yellow fever was formerly prevalent, one was positive, of 821 from persons under twenty years of age in various parts of the West Indies, Barbados, Cuba, Jamaica, Porto Rico, St. Lucia and Trinidad none was positive, but thirty (out of a total not stated) of those over twenty years were positive. From Mexico 1089 sera were tested of those above twenty years old 43 per cent were positive, but of those between five and nine years only 0.9 per cent. Of sera taken from subjects under twenty years of age in Panama and Costa Rica all were negative.

With regard to the findings for South America—Brazil, Paraguay, Bolivia, Chile, Peru, Ecuador, Colombia, Venezuela, British, Dutch and French Guiana—of the world survey of immunity distribution Dr. Soper concludes that the reported incidence, that is clinical cases, is no safe index of the occurrence of the disease in endemic zones and that, though outbreaks may come to an end, there is a large silent area of infection in the interior. Endemicity is not limited, as was believed, to the coast of north and east Brazil, but extends to Bolivia, Paraguay, Peru, Ecuador, Colombia and Venezuela, and is present in many districts in which there is no *Aedes aegypti*.

Though the protection test seems to be quite reliable for human sera the same cannot be said regarding those from animals. Thus, among sera of 83 cows from West and East Africa and Anglo-Egyptian Sudan examined by Findlay and MacCallum, 16 (19 per cent) gave protection. Human sera from the same regions were also protective. Of 82 cows' sera from Kenya, where human cases of the disease are not known, 11 were positive, and of 70 sheep sera from Kenya three were positive. In view of these peculiar findings Findlay and MacCallum examined sera from 40 Himalayan cows and found three positive, two of these were retested later and one still gave a positive. Finally, 153 sera of cows in England and France were examined and one of these reacted, five months later, however, this was negative.

Interpretation of these anomalies is not easy. In the yellow-fever districts of Africa the cattle may have become infected by the virus and discrepancies between the findings in human and animal sera be explained if the vectors were zoophilic rather than anthropophilic. Indian cattle, on the other hand, could not have been exposed to infection by yellow fever. We must, therefore, be cautious in interpreting the results of the test when applied to animal sera. (See above, p 418)

It will have been gathered from the foregoing that the subject of yellow-fever research owes much to the staff of the International Health Division of the Rockefeller Foundation. Their activities in 1936 comprised co-operation with the National Health Department of Brazil in investigation and control, with the corresponding department of Colombia, with surveys and control in various South American countries, with prosecution of research at their New York laboratories, and finally the co-operation at Entebbe where, by arrangement between the Colonial Office, London, and the International Health Division of the Foundation a Yellow Fever Research Institute is now established. Formerly, this building was used as the Human Trypanosomiasis Institute.

The Foundation has been very fortunate in that they have had only one fatal accidental infection of a member of their staff in the field, namely, Howard B. Cross, who died in Mexico in 1921, whereas among scientists engaged in the West African Yellow Fever Commission Adrian Stokes in 1927, Hideyo Noguchi (1928), William Alexander Young (1928) and Theodore B. Hayne (1930) died of the disease and Paul Lewis (1929) died of the infection contracted at the Division laboratory, Bahia, Brazil. Others engaged in the investigation, Maurice Wakeman, Nelson C. Davis and Wray Lloyd died from other causes.

But the sacrifice of the lives of Lazear in 1900, Cross, Stokes, Noguchi and the rest will never hold back others and we may safely say that "those who see in medical research a noble opportunity of benefiting their kind and those who find in it the risk and glamour of high adventure" will ever be attracted to problems such as this.

10 THE PLACE OF ORIGIN OF YELLOW FEVER

In the foregoing pages we have endeavoured to place before the reader an historical account of yellow fever, the most notable of the recorded outbreaks, the mode of its transmission, the results of application of knowledge so obtained, the nature of the *causa*

causans, experimental work with the virus, the preparation of material for conferring immunity artificially, studies in natural immunity and, by the application of this knowledge, the mapping out, by retrospective diagnosis, of recent or present endemic sites. We are now in possession of certain facts by which we are able to consider the vexed and still undecided question as to the place of origin of yellow fever, so far as history can assist us.

Much of the evidence on which opinion can be expressed has already been given in the opening sections dealing with the historical accounts of outbreaks of the disease in different parts of the world, and for the details of these reference must be made to those sections. Here we shall attempt to marshal the evidence for and against the Old or the New World origin of the infection.

At the very outset we are confronted with a difficulty, for all the evidence on which we have to rely is clinical, and the earliest describers were pioneers, fighters and explorers, not medical men, chroniclers such as Herrera, Dutertre and Rochefort, whose aim was to describe military matters and they speak of medical concerns only when these interfered with their projects of conquest. Hence, diagnosis is vague even when they use terms which we to-day can understand and yellow fever was not distinguished from certain forms of malaria, from typhus, from relapsing fever and so on. The difficulty is even greater when they use the local terms for diseases they encountered and we are left to interpret vague accounts of symptoms, written by laymen, into their modern medical equivalents. We need not repeat what has been said already concerning these (see p. 282-4), but there was a disease which was epidemic in early days in Mexico, denominated *matlazahuatl*, which some authorities maintain to have been yellow fever. So far as we have been able to ascertain, however, the natives were almost exclusively attacked, it prevailed more in the interior of Mexico than in the coastal regions—these points militating strongly against yellow fever. As we have already mentioned, the epidemics recorded under the names *papera*, *tabardillo*, *tohtommaliztli* were not yellow fever but diphtheria or mumps, typhus and smallpox respectively. We have no proof that the conditions described under the names *cocoliztli*, *xekik*, *modorra* and even *coup de barre* were yellow fever.

If we attempt to decide the question on dates of records we are likely to stray. There are writings rendering the diagnosis certain in America as early as 1648, that is earlier than any we have of West Africa, but we must not place much reliance on such evidence, for the early history of America and of settlements,

Spanish or other, is fairly detailed, whereas it is quite otherwise as regards Africa. The early European settlements in West Africa were trading-posts and epidemics among them would not attract notice, even if they arose, because the number of Europeans was small, hence, mention of diseases clinically differing from yellow fever, or failure to mention anything interpretable as yellow fever, may be said to be a feature or characteristic of New World history distinguishing it from that of West Africa. Thus, in early records of what was almost certainly yellow fever in Yucatán, Mexico, we find that negroes suffered practically equally with Europeans. If the negroes were imported slaves who had been exposed to yellow fever in their own country the incidence among them would be small compared with that among the Europeans. The conclusion, therefore, must be either that the negroes referred to were not imported slaves, or that, if they were and were equally susceptible, this would be in favour of American as against West African origin. On the other hand, in favour of African origin are, firstly, the reaction of the negro to yellow fever is often and, in the young, more usually mild, and, secondly, the number of susceptible whites was small, and, thirdly, malaria was often very severe and might not be differentiated from yellow fever even amongst whites, and, in fact, was not till Schotte's classical account of the St. Louis (Senegal) outbreak in 1778, and even he, when describing an outbreak of yellow fever among British troops, considered it as intensified malaria. So, although Cogolludo's description of the disease in America, in 1648, preceded Schotte's description of it in Africa by 130 years, this has not much weight, because the American Indian was as susceptible as the white man, whereas the West Coast African seems to have been, as far as we can trace the records, absolutely or relatively immune, secondly, failure to describe it earlier in Africa can be explained by the paucity of Europeans, and most of them (soldiers or those sent there as convicts) were incapable of describing it, thirdly, in the young the disease was mild and often escaped recognition among those on the coast, and among slaves brought from the hinterland it was probably confused with other fevers and with scurvy.

Ancient African history, that is of those parts where records of events were made, is of no help in determining the point either way, for though we have good histories to refer to of Egypt, Nubia, Ethiopia, the Barbary States, they relate to those parts of the Continent where, even in more modern times, yellow fever has not become established. The Phœnicians visited the Gold Coast,

and Hanno of Carthage explored as far as the 'Southern Horn,' probably the modern Sherboro Island, Sierra Leone, but beyond the fact that they did not land there, still less stay, we know nothing but that they were frightened by and afraid of the natives who spent much of the night in drum-beating and noisy orgies

The fundamental points may be succinctly stated thus

1 *The disease was recognized in America earlier than in Africa*

As already stated the first account of yellow fever in the New World was that of a Yucatán outbreak in 1648, in West Africa by Schotte (and mentioned by Lind) of the Senegal outbreak in 1778. But communication between Africa and the New World was frequent during the two centuries preceding Cogolludo's account, indeed, in 1503, Ovando, the Governor of Hispaniola, asked that no more negroes might be sent as they were "already too numerous for good order." The belief of earlier writers that yellow fever was endemic in Haiti before the coming of the Spaniards in 1492 has been referred to already and also the sickness among Columbus's troops in 1493 and again in 1495, and at Darien, 1511-14.

2 *The reaction of the Negro to infection*

The West African had it mildly and rarely died of it, whereas the American Indian exhibited no immunity, but contracted it as readily and had as high a fatality rate as the white man.

3 *Species of Aedes*

There are several species in West Africa, widespread and in nearly every village, in America practically only one, most abundant in or close to seaports.

4 *Conditions necessary for the continued existence of Yellow Fever*

Such are the presence of the virus, indigenous or introduced, prevalence of *Aedes* and existence of susceptibles. The only places in the New World, prior to its discovery by Columbus (Friday, 12th October, 1492) fulfilling these postulates were (i) The *Tierra caliente* of Mexico—the Gulf Coast, (ii) Yucatán and Central America, (iii) The coast of Peru, especially around Trujillo, (iv) Scattered islands of the Caribbean, linked to one another and to the mainland by travel, along the Isthmus of Panama. The last of these is improbable because the population of each was small and later, after the Europeans had settled in them, yellow fever attacked them and died out more than once.

The third we can eliminate firstly, because of its isolation, secondly, because its history is well known and no mention is made of any epidemic outbreak there

Carlos Finlay, summing up the evidence available in 1880 and the immediately following years, concludes that

- (1) Before the Spanish discovery of America yellow fever was endemic on the coast of Mexico, especially at Vera Cruz, Darien and Nombre de Dios
- (2) The Caribs in travelling from the latter would bring infection to the Lesser Antilles and so set up fresh epidemics, when there were sufficient susceptibles
- (3) Cuba was free from yellow fever in the first 138 years of Spanish occupation, in fact till, in 1649, infection was imported from the neighbouring continent, probably from Mexico
- (4) Porto Rico, Jamaica, and other islands were free from yellow fever when first occupied by the Spaniards

Next, does the history of the slave trade give us any help in solving the problem ? The larger question of the trade and disease is dealt with subsequently, here we are considering it merely for any light it may throw on the place of origin of yellow fever. The source whence most of the slaves were obtained was the mainland, the trade being started by the Portuguese in 1441. Seven years later they built a fort in the Bay of Argum just south of Cape Blanco as a base for the trade and in 1482 and 1490 at Elmina and Angola respectively which became the centres of collection, later they were brought from the Benin district. Their ultimate destination was, of course, tropical America and the Spanish settlements.

At first only Portuguese vessels were allowed to enter the ports of West Africa belonging to Portugal and only Spanish vessels were allowed to trade with the Spanish ports of America. We must remember that between 1581 and 1640, and only during that period, were Spain and Portugal under the same crown. São Thiago, in the Cape Verde Islands, was therefore decided upon as a convenient intermediate distributing centre. Slaves taken from ports not under Portuguese control were sent to the French, Dutch, and English colonies in America.

Now *Aedes* might easily be imported to São Thiago from the Guinea Coast, the drinking water was rain which was stored on

board and in the dwellings and afforded abundant opportunity and sites for breeding. At present, at all events, *Aedes* abounds there. The Cape Verde Islands in Elizabeth's time were notoriously unhealthy. Sir Richard Hawkins says of them "In two times that I have been in them, either cost us one half of our people with fevers and fluxes of sundry kinds and in one of them it cost me six months sickness with no small hazard of life." There is considerable probability, amounting almost to certainty, that the disease which proved so disastrous to Drake's expedition at São Thiago in 1585 was yellow fever. He landed a thousand men and stayed there ten days. Soon after putting to sea again his men fell sick and many died, that is, we have evidence of a disease with a high fatality rate prevailing among men who a few days before had been on shore or on ships near the shore, and, being previously in good health, must have contracted it at the port, and, clinically, the disease was characterized by fever and later the presence of petechiæ. Similar records were given by other commanders of expeditions, Menezes in 1624 and Mascharenas in 1638.

These records of sickness among members of expeditions and voyages of discovery do not assist us much, though in the aggregate their evidence is of some value. Records of sickness were made only if it affected the progress or interfered with success of the venture. But examination of the logs of ships returning from the West Coast give unwitting information when we read "many deaths, sometimes three or four a day", and "out of 140 scarcely 40 returned to Plymouth", this was written in the log of a vessel coming home from Benin.

When in 1581 and during the ensuing sixty years Spain and Portugal were under one ruler, restrictions against the Portuguese having commerce with the Canary Islands were removed [incidentally the Canaries were so named, not on account of the birds but because of the dogs (*canis*)]. Then both nations brought slaves from São Thiago and the Guinea Coast to the Canaries, which became the ports of call between the Peninsula and Africa. The Canary Islands inhabitants were susceptible to yellow-fever infection and epidemics of the disease occurred there after 1641, perhaps earlier, but certainly in the opening years of the eighteenth century. Reference has already been made to the Van der Does expedition of 1599, when at São Thomé a thousand sailors and the Commander-in-chief died.

Again, in the Gambia there have been epidemics of fever for nearly 500 years, we cannot say whether the earlier outbreaks

were yellow fever, but so far as we can find from the records there has been no change in their general character either before or after the discovery of America, before or after the slave trade started, or before and after the introduction of cinchona as the best form of treatment of tropical fevers

On the coasts of the Gulf of Guinea from Sierra Leone to the mouth of the Congo the disease has been almost continuously endemic since it was first reported there as Bulam fever in 1793, although there has been practically no change in the general conditions of settled towns, the presence of *Aedes*, continued trading and inter-communication. Information gained from modern methods of research and their epidemiological interpretation will be given elsewhere, from the historical aspect it is well to marshal the evidence chronologically and prior to the application of modern research methods on immunity the only criterion we had that a locality had not previously suffered from yellow fever, for a long time at least, was the aptitude manifested by the generality of the population to contract it when the infection was introduced. Thus, for 138 years after Cuba was occupied we hear nothing of yellow-fever outbreaks and any epidemics we know of seem to have been smallpox, but when in 1649 yellow fever was introduced from the mainland it raged, producing terrible havoc and causing many deaths, among the indigens as well as foreigners

Further evidence of yellow fever in the early days of available records being new to the West is the fact that the local people had no name for it, but called it by the name of the place from which it was brought, *e.g.* Olinda fever, Oriflamme fever (from the name of the vessel introducing infection), Mal de Siam, Bulam fever, Chapetonada (*i.e.* disease attacking *chapetones* or newly arrived Europeans)

Modern facilities for testing immunity reactions—the mouse-protection test in particular—have thrown light upon the question of place of origin and present existence, and based upon these the following points must be taken into account when considering the former

1 In Africa immune persons have been found between latitudes 15° N and 5° S on the coast and over a district extending inland as far east as Bahr-el-Ghazal in the Anglo-Egyptian Sudan, although we have no evidence whatever indicative of recent introduction of infection there. In the Nuba Mountain district, north-east of Bahr-el-Ghazal Province positive findings were obtained in several districts, in Kau as high as 78 per cent, yet no

connection could be traced with any disease in the past resembling yellow fever clinically. A similar state of things was reported previously in Upper Ubangi, in Equatorial Africa, where an even higher percentage of 98 was found.

New information was obtained also from the Belgian Congo, some who had negative sera on a former testing proved positive two years later, although no disease suggestive clinically of yellow fever had occurred in the interval. The findings in Libenge before and after an outbreak of what was thought to be 'infective jaundice' have been noted already. These facts point to the necessity, at least advisability, of retesting at intervals the sera of those living in a district or area in which a few positive results have been obtained.

On the other hand, yellow fever has occurred in parts of South America far removed from seaports, and townships along the valleys of the great rivers have suffered from outbreaks and cases have been met with even in the mountainous regions.

2 The mild reaction of infectable and infected African contacts, exposure to infection over a long period, with elimination of the more susceptible and thereby a gradual acquirement of racial resistance.

Against this must be noted the facts that among Africans the attacks are not always mild, and in South America, among persons of mixed European and Indian descent 'inapparent' infections are by no means rare, but fewer American negroes than African show immunity.

3 There is similar evidence of long exposure to infection among African monkeys. Though yellow fever is not known clinically in East Africa the monkeys there are no more susceptible than those of West Africa where the disease is known to have existed for centuries. Moreover, *Aedes ægypti* is not found in certain parts of South America although yellow fever is known there, the virus may be transmitted by the indigenous species, *Aedes scapularis*.

It is possible, of course, that there are two strains of virus, that of the Old World and that of the New, though, if this be so, the differences are not demonstrable by any of the means known to us at present—in fact, what evidence we have all tends to show the identity of American and African strains.

As long ago as 1842 Dr R. R. Madden, a commissioner appointed to report on the climate of the West Coast of Africa, stated

I would defy any man to point out the difference between the cases of yellow fever as they exist in Cuba or Jamaica, and those of African local fever as it exists on the West Coast. Of the identity of

West Indian yellow fever and African local fever I have no doubt my acquaintance with them has unfortunately been of too intimate and personal a kind to leave me in ignorance of the similar symptoms and character of both

In his day, of course, he had only the clinical aspect by which

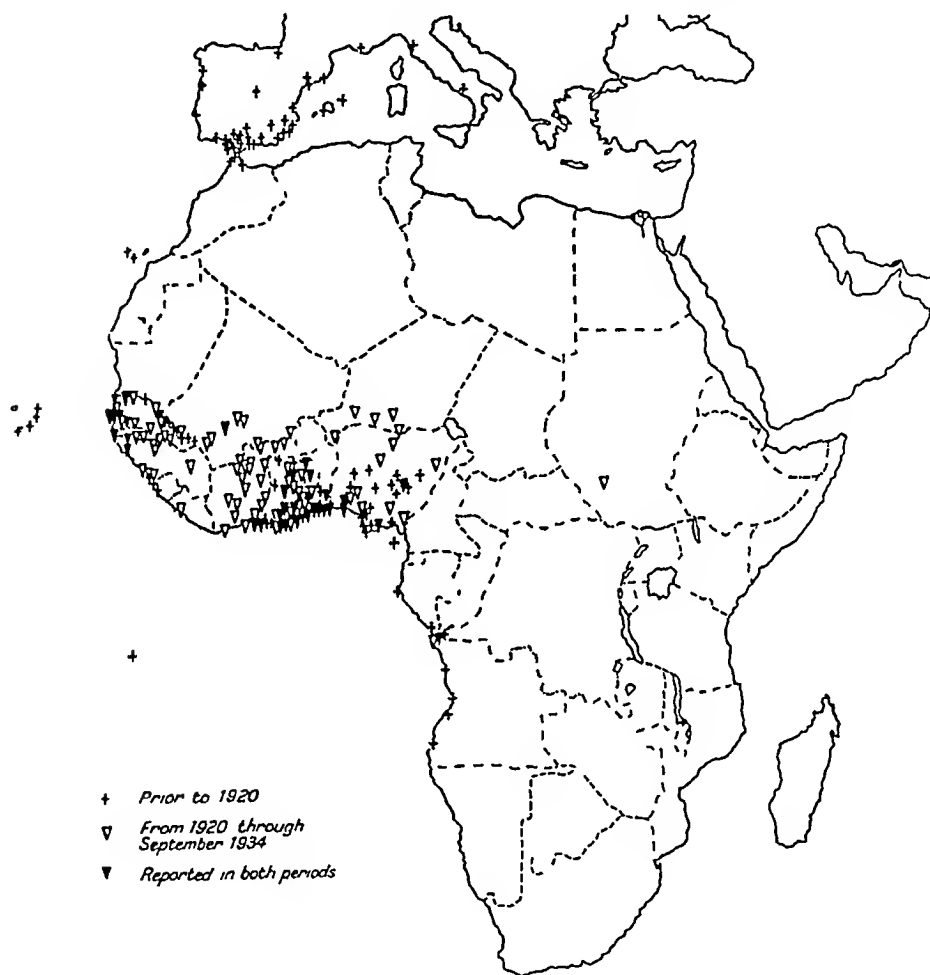


FIG 6

Places in Africa and Southern Europe in which yellow-fever cases were reported, classified as to occurrence before or after 1st January, 1920

Reproduced by kind permission of Dr Wilbur A Sawyer

to judge There may be even a third strain, the jungle type transmitted, we know not how, possibly by non-domestic *Aedes*

Examination of the blood of Amazon Indians in the, at present, unexplored forests north of Matto Grosso might help considerably in determining whether a primary New World strain exists There is, again, another possibility, that the virus was present in monkeys

in both continents before human beings settled there. The question of man being an accidental host has been referred to already.

From the evidence, mostly clinical and epidemiological, avail-

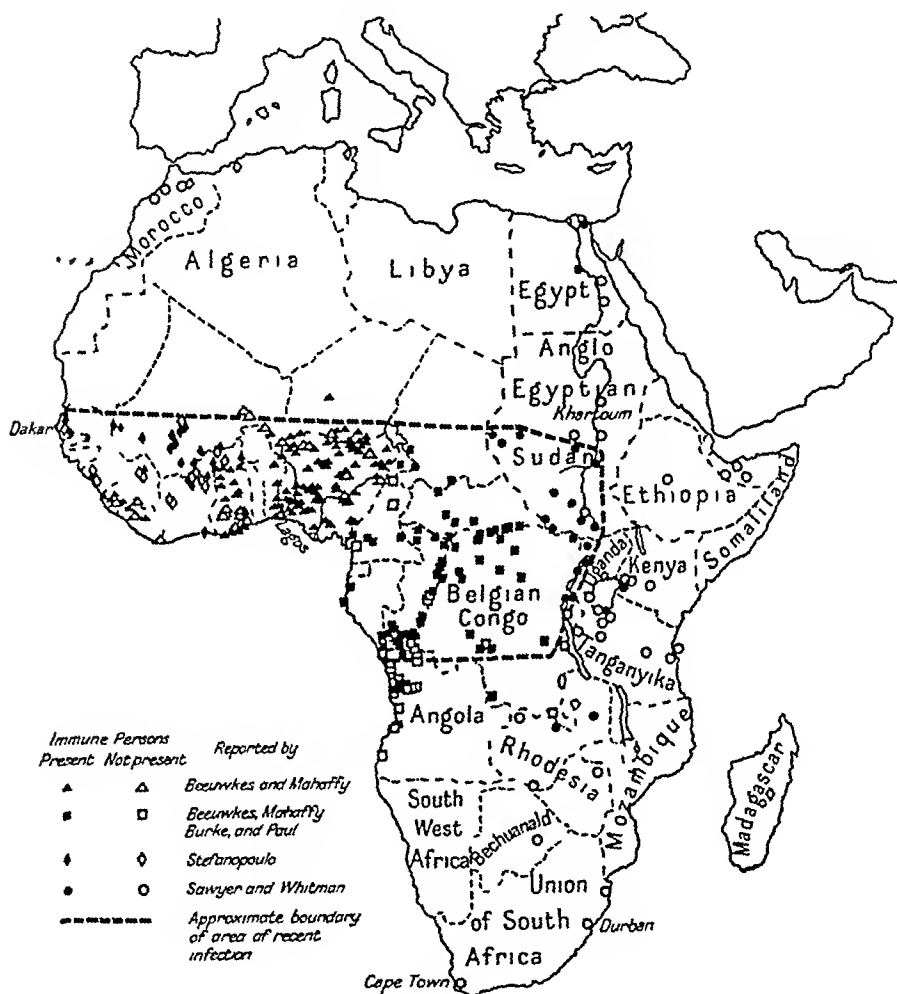


FIG 7

Places in Africa classified according to the presence or absence of persons immune to yellow fever, as demonstrated by protection tests in mice in surveys from 1931 to 1934

Reproduced by kind permission of Dr Wilbur A. Sawyer

able in the 'eighties of last century, Hirsch sums up more in favour of the western hemisphere as the place of origin, he says "We find throughout the whole of the yellow fever region only *three* situations at which the disease bears an undoubtedly endemic character—the West Indies, the Mexican Gulf Coast, and part of the Guinea Coast" Heinemann in 1879 mentioned five places

on the coast of the Mexican Gulf and adds that these are not 'original endemic' places, but became so after infection had been repeatedly imported from Cuba

As for the Guinea Coast he regards Sierra Leone as the original endemic focus, but against this being the original home of yellow fever, as Pym and others state [with "no reason at all," says Hirsch], are the facts that accounts of yellow fever on the West Coast of Africa do not date beyond the eighteenth century and he maintains, therefore, that it is more probable that this region was infected from the Antilles, and became an endemic focus later when the disease had acquired naturalization. This question of priority of written record has already been considered (see pp 441, *et seq*)

How fallacious it is to rely on clinical cases only or reported instances of the disease is made very apparent if we compare the two maps given in Dr W A Sawyer's Harvey Lectures in 1934-5. The first shows the places in Africa (and southern Europe) from which cases of yellow fever had been reported, the second indicating the presence or absence of persons immune to the infection, as demonstrated by the mouse-protection test. There is no need to enlarge on this, they themselves tell the tale more graphically than a page of text. Suffice it to say that, although prior to 1920 the disease had not been reported east and south of Nigeria except in a few places on the Atlantic Coast and on the lower Congo, the survey revealed the presence of immune persons in an area extending from Nigeria to the Nile in the Anglo-Egyptian Sudan, and from the desert in the north throughout the Belgian Congo on the south.

Again, in the French expedition to Mexico in 1862 the troops from Kordofan proved to be almost immune, cases among them were few and mild, whereas the rest of the troops suffered severely. This fact led Carter to infer that the negro had a true racial resistance or reduction of susceptibility to yellow fever.

At that time and even later [says Sawyer] there was reason to think that yellow fever had never been within a thousand miles of Kordofan, but the subsequent revelations of the immunity survey showed that the infection must have been recently in the province without establishing a recognized epidemic.

It follows that these men of Kordofan had acquired their immunity as far back as 1862 at least.

The immunity survey has shown Asia and Australia to be free, the results of tests in the Western Hemisphere are shown in the map reproduced from Dr Sawyer's lectures. Outbreaks were

frequent in the United States in the eighteenth and nineteenth centuries (see Table, p 326 *et seq*), but there has been no known

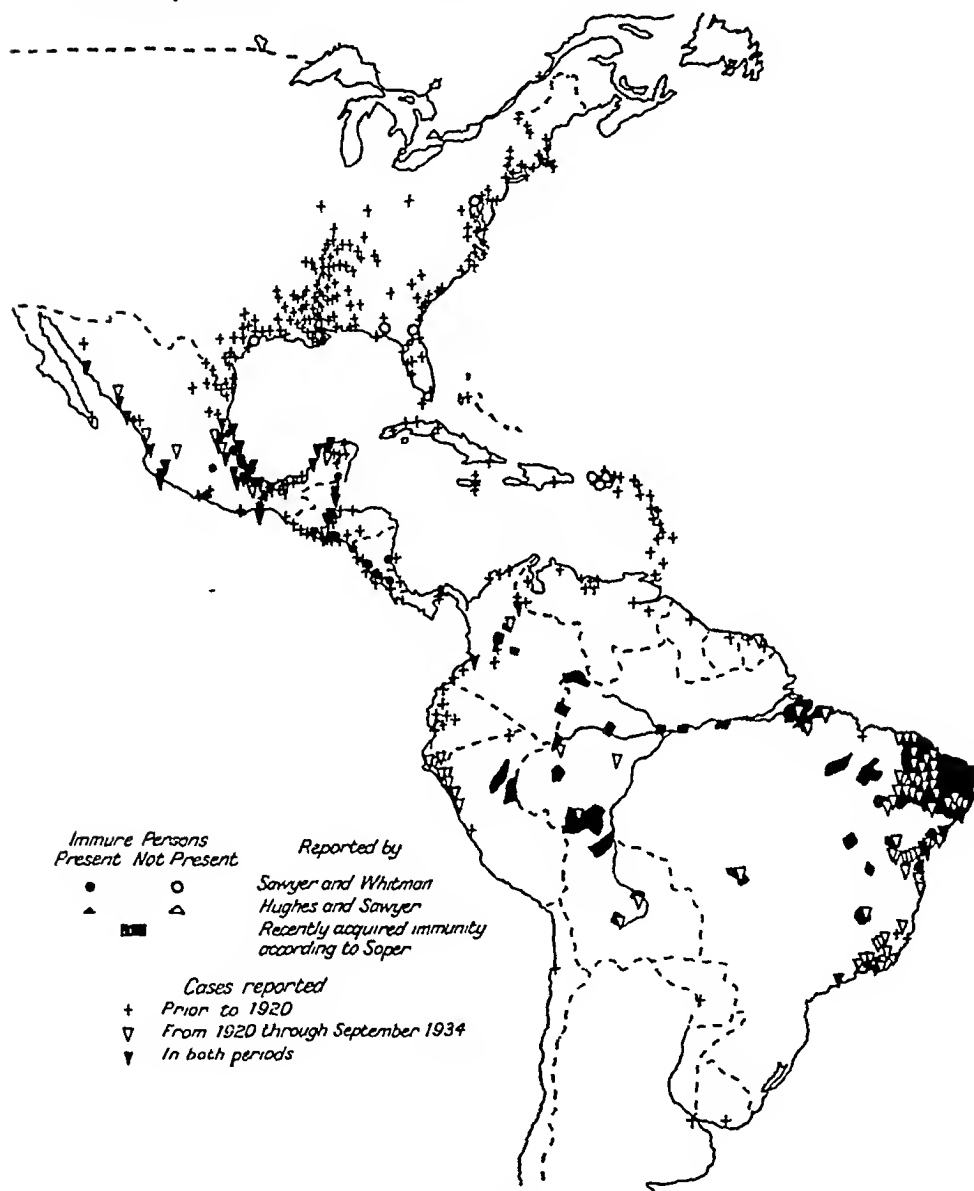


FIG 8

Yellow fever immunity and cases in the Western Hemisphere

Reproduced, by kind permission of Dr Wilbur A Sawyer, from his Harvey Lectures, 1934-1935

outbreak there for more than thirty years and no immunes have been found there or in Canada among the sera tested In Mexico and South America outbreaks have occurred so recently that

infection may still exist there, the outbreak in Salvador in 1924, it is thought, probably started from a pre-existing unrecognized infection, it was certainly active in Mexico in 1920 and in Tampico two years later

The value of the immunity test has again been exemplified in the Amazon Valley. The disease was thought to have disappeared from the valley above Pará since 1913, but the tests have proved that many of those born since then are immune and the viscerotome affords corroborative evidence that the disease occurs even now [the record was made in 1935]. Two epidemics in Bolivia and another in Matto Grosso probably originated in a 'silent focus'. Attention may here be again directed to what has been stated regarding the recent Magdalena Valley outbreaks which the protective test has proved to be yellow fever.

The reader will gather from the foregoing that the evidence at our disposal is not enough for an indisputable decision to be given as to the place of origin of yellow fever. Fairly strong arguments can be marshalled on either side, only to be met by equally potent ones on the other, but on the whole the greater weight would appear to be on the side of Africa.

In conclusion, the position of affairs in our own day has been ably summed up by Dr Wilbur A. Sawyer in the lectures to which we have already referred. He says

Yellow Fever has been present in recent years in most of the coastal region of Brazil from Rio de Janeiro to Pará and is now wandering about in the Amazon Valley and the adjacent areas of the Magdalena and Orinoco watersheds, under conditions as yet unknown, and its range includes parts of Brazil, Colombia, Bolivia and Peru.

We see that infections too mild to be recognized clinically, and therefore not reported, but nevertheless capable of conferring immunity, may be prevalent in silent areas for decades, and also in epidemics definitely recognized as yellow fever, mild and missed cases must often far outnumber those diagnosed. All, we think, will agree with Dr Sawyer that

It is difficult to account for the persistence and wide extent of yellow fever infection in some tropical regions in view of its easy control or spontaneous disappearance in others. Differences in meteorological conditions or density of population are not alone adequate explanations.

Among the possible influencing factors is the presence in some regions of insect vectors other than *Aedes aegypti*. It has been shown in laboratory experiments by various workers that fourteen species of mosquitoes in addition to *A. aegypti* are capable of transmitting yellow fever by bite—eight in Africa, five in South America, and one in the

East Indies The search for new vectors has become of more than academic interest since Soper, Penna, Cardoso, Serafim, Frobisher and Pinheiro (1933) showed that a rural epidemic of proven yellow fever actually did occur in Brazil in the complete absence of *A. ægypti*. Epidemics without *A. ægypti* have since been encountered in Bolivia and Colombia.

Attention has been called more than once in previous pages to the readiness with which monkeys can be infected with the virus of yellow fever, and also to the fact that many of these animals have been found in nature to be immune by protective tests. That the wild monkey might be a reservoir of the virus was mentioned by Balfour in 1914 (*Lancet*, p. 1176). Among the natives of Trinidad there existed a belief that an outbreak of yellow fever was preceded by some fatal epidemic among red howler monkeys and he quoted by way of illustration the outbreak at Brighton in the south-east of Trinidad where this was observed. It is only right to add, however, that in this instance at least fresh importation was not ruled out and we have noted already the easy possibilities of introduction of the infection into Trinidad (p. 300).

Erinaceus (hedgehog) is another animal found susceptible, and in jungle yellow fever the opossum (Didelphys), and further study may discover yet others. The upshot of this is that other reservoir hosts may exist in nature, comparable to game and trypanosomes in Africa, from which some insect other than *Aedes ægypti* may infect man.

Our present-day knowledge in general terms can be epitomized in a few sentences. We know of two extensive regions within which yellow fever is endemic, one in Africa, the other in South America, beyond which the disease, at least in epidemic form, is rarely if ever encountered, while within them are districts where the disease occurs although no *Aedes ægypti* can be found. This being so, the methods which have proved so pre-eminently successful in eradicating the disease from urban centres, by application of the measures based on eliminating the mosquito vector or protecting man from the vector and the mosquito from man, fail to prevent the disease in rural, jungle areas, we know also that infection introduced from such an area may start an urban outbreak if the vector is allowed to flourish and that the only certain method of protection to render us independent of these outside influences is by inoculation. If these measures are borne in mind and acted upon, yellow fever need never again be the source of alarm as it was of old.

CHAPTER VIII

HUMAN TRYPANOSOMIASIS

AFRICAN TRYPANOSOMIASIS

I INTRODUCTION

Human trypanosomiasis and sleeping sickness are often regarded as synonymous, but this only applies if restricted to African trypanosomiasis. Human trypanosomiasis in America is not characterized by lethargy.

Trypanosomal infection of animals was known many years before the discovery that these protozoa could cause disease in man, nevertheless sleeping sickness in man was known centuries before the discovery that trypanosomes caused disease in animals.

Dr Meyerhof of Cairo has recently drawn attention to a letter written to the *Egyptian Gazette* (December 1931) by H R H Prince Omar Tussîm, who took no little interest in ancient Arabic literature and had noted that the disease was mentioned by an Arab writer of the fourteenth century, Al-Qualquashaudî, when recording the rulers of the Mâlli Kingdom in that and the preceding century. Referring to Mârî Jâza, the second Sultan, he states

His end was to be overtaken by the sleeping sickness ('illat an-nawm) which is a disease that frequently befalls the inhabitants of those countries, and especially their chieftains. Sleep overtakes one of them in such a manner that it is hardly possible to awake him. He (the King) remained in this condition during two years until he died in the year 775 A H (A D 1373-4).

Judging from the words "a disease that frequently befalls the inhabitants" we may infer that it was not a new condition, although no mention seems to have been made of it by earlier writers in the Sudan. The Mâlli, or Mandingo, rule began to decline during the following century and in the seventeenth was overthrown finally by the Bambara tribes. Not long ago the ruins of two capitals of the Mâlli Kingdom were discovered in the Western Sudan on the banks of the Niger and Sankarani rivers.

The Arabs were the early colonizers of Africa, they were

driven out by the Bantus from much of the territory they had settled, retaining only the coastline of the south-east till the arrival of the Portuguese in the fifteenth century. That they had not extended their borders more widely is now thought to have been due to interference and difficulty of transport owing to ravages of the tsetse fly. In the sixteenth century the Portuguese lost a large number of their horses and camels which accompanied them in a powerful expedition into East Africa, they ascribed this loss to poisoning of the wells by the Arabs, but it is more probable that the tsetse and trypanosomiasis were the cause.

We must, however, leave speculation and come to the greater certainty of times less remote. It is a well-known fact that, prior to the building of railways, opening up of Africa was greatly hampered by the ravages of the tsetse. As soon as an expedition started to penetrate the interior the fly would attack the cattle transport and after a short time the expedition would return, with even greater difficulties, from reduced transport, to its base. Thus, cattle transport came to be out of the question, to penetrate and explore the country it was necessary to go on foot with native portage.

Though the tsetse was a veritable scourge and though animals, in particular transport animals, cattle and horses, were known to die in large numbers from a definite disease, for a long time no interconnection was thought of. Livingstone in his travels notes that "the cattle in rushing along the water in the Matabe probably crossed a small patch of trees containing tsetse, an insect which was shortly to become a perfect pest to us." There may be noted, even at this stage, the three points favouring tsetse—trees and shade, proximity to water, and the presence of cattle.

To treat the subject of trypanosomiasis historically—a disease in which human and veterinary investigations have gone on simultaneously and have been of great mutual assistance—we must give a sketch, as nearly as the subject will permit, in chronological sequence. At the beginning of this chapter we mentioned that sleeping sickness in man—negro lethargy, *maladie de sommeil*, *somnolenza*, *laloregolo*, *nelavane*—was recognized (though not its cause) before trypanosomes were known to cause disease in animals—dourine in horses, nagana in horses and cattle, surra in horses and camels, for example. We will, therefore, speak first of the human disease.

The earliest known account of the condition is that by John

Atkins, an English naval surgeon who was on the Guinea Coast in 1721. In *The Navy Surgeon*, 1734, he gives a short description of the 'sleeping distemper,' so-called because it was characterized by somnolence, common among the negroes of the "coast of Guiney." He noticed that young persons were more liable to attack than the old and that the fatality rate was high, if recovery took place the patients "lose the little reason they have and turn idiots."

We hear no more of the condition—at least the author has not been able to find any further record—till sixty years later, when Winterbottom, practising in West Africa, describes what he calls *lethargus* as occurring among the inhabitants of the Bight of Benin, "a species of lethargy which they [the natives] are much afraid of, as it proves fatal in every instance." He drew attention to the cervical adenitis in the earlier stages preceding the somnolence and debility and stated that the slave-dealers would not buy any showing these enlarged glands, regarding them as predisposing to the lethargy. If any such were bought or captured they were got rid of as quickly as possible, for "even the repeated application of a whip, a remedy which has been frequently used, is hardly sufficient to keep the poor wretch awake." The acumen of the natives' observation is evidenced by the fact that the Mandingoes in the Gambia used to "cut the neck-stones of the boys to prevent the occurrence of sleeping sickness in later life." In spite of all care on the part of the slave-traders patients in early stages might be shipped, for Moreau de Jonnés in 1808 noted its existence among slaves in the Antilles and as there are no tsetse there local spread was out of the question (see later).

The next to contribute to our knowledge was Robert Clarke who in 1840 gave a fairly detailed account based on his observations of cases seen by him in Sierra Leone, and called it "narcotic dropsy." In his view it was more common in the interior than on the coast. Slaves were more often, in fact usually, captured in the interior, and Guérin of Martinique in his Paris thesis, 1869, recorded the existence of 148 cases on the estates among slaves who had been imported from the Congo district, only one recovered. Before him, however, other French doctors had seen cases in the West Indies. Dangaix in 1861, Nicolas, Gaigneron and Griffon du Bellay in 1863. Naturally, as we know now, the disease did not spread there, owing to absence of *Glossina* from the West Indies, and no Creoles ever were attacked. These early observers attributed the listlessness, melancholy and lethargy to homesickness. Gore, writing to the *British Medical Journal* in

1875, and soon after him Corré in the *Gazette Médicale de Paris*, 1876, note the frequency with which enlargement of the cervical glands occurs and the latter lays stress on this as a symptom. Corré was a French naval surgeon and told how in Lower Senegal the *maladie de sommeil* decimated some of the smaller garrisons. He tried to study the disease from its epidemiological aspect, to correlate the climate, the water-supply, the food and general state of the people, and he came to the conclusion that cases were most frequent near water and that drainage of the land and agricultural undertakings prevented it, though he failed to connect it with the prevalence of insects.

Other names for the disease were *laloregolo* and *nelavane*, and it is under the latter, local, name that Corré speaks of sleeping sickness as having led to some villages being abandoned and others being in a neglected state, ill-kept, surrounded and encroached upon by jungle and dense bush, and inhabited by a 'lazy' people whose numbers were rapidly diminishing. The natives, it would appear, were aware of the long incubation period and did not consider a man free from the disease until he had been seven years away from an infected locality. For many years it was believed that none but natives were susceptible, or were attacked, but Père Labat early in the eighteenth century speaks of a European suffering from symptoms very like those of *nelavane*.

The first known case recorded in Angola was reported in 1871, but thereafter cases were many, deaths common and several prosperous villages had to be abandoned. The Portuguese Government thereupon sent out a scientific commission to investigate, but beyond noting the important significance of the cervical adenitis as pathognomonic in a *somnolencia* district, they came to no satisfactory conclusion. We may anticipate here a little by remarking that when, early in the present century, the findings of Dutton and Bruce were published, blood films of twelve patients which had been taken by members of this Portuguese Commission were re-examined, and the presence of trypanosomes, which they had overlooked or disregarded, was confirmed.

Even in the last twenty years of the nineteenth century certain districts were known to be endemic foci of the disease, the natives knew it well in the Congo as far as the Stanley Pools in 1885. Mission stations suffered severely because the natives, recognizing the earlier stages of the disease, would bring the stricken to the missions and hand them over. In time, these stations, like the stricken native villages, had to be abandoned on account of the number of fatal cases among the new converts, some recording

300 and one as many as 600 deaths. In the last quinquennium of last century and the first of the present it is calculated that deaths from this disease in the Congo had numbered at least half a million.

The advent of Europeans, by opening up new territories, by extending trade and commerce and facilitating travel, undoubtedly aided in spreading infection beyond the former limits. By 1880 the distribution was known to include a large part of the West Coast between Senegal and the Congo—Senegambia, Sierra Leone, Liberia, the Ivory and Gold Coasts. No mention is to be found at that time of its existence in Uganda or elsewhere in East Africa. Cases had been reported from Guadeloupe and Martinique, and the Bahamas and Brazil among imported negroes. In less than half a century after, its area of prevalence in Africa had spread widely and included the Gold Coast, Nigeria, the Cameroons, Portuguese Guinea, Spanish Guinea, French Equatorial Africa, the Belgian Congo, Portuguese Congo, Anglo-Egyptian Sudan, Uganda, Tanganyika, Nyasaland, Rhodesia, Bechuanaland and Mozambique.

Introduction from West Africa to the East seems to have taken place at the end of the nineteenth century and, at the beginning of the twentieth, a severe epidemic raged round the shores of Lake Victoria. Dr Mense is of the opinion that Henry Stanley, the explorer, was an unwitting agent in the spread of sleeping sickness. In 1887 he started on the Emin Pasha Relief Expedition up the Congo with a company of over 700 Zanzibar porters, Somalis and Sudanese soldiers for the equatorial province of Upper Egypt. He met Emin Pasha at Wadelai on the shore of Lake Albert Nyanza. Travelling with his hired carriers from the Lower and Middle Congo to the Nile, Stanley undoubtedly brought infected men to the Lake region. It is equally probable that Emin Pasha's men brought it also themselves from the Congo. The remnants of Emin's army and the camp followers and the soldiers' wives and children settled in Uganda and Busoga, and there is no evidence that the disease was known there at that time, but in 1901 Dr (now Sir) Albert Cook, of the Church Missionary Society, reported its presence and believed that the infection had been introduced by these settlers. On hearing of this, Dr Hodges, who was a recently appointed medical officer for Busoga, inquired into the matter and found evidence of the existence of the disease in one district on the Lake shore and the islands for the previous six years and that hundreds of natives had died of it. Seven years later, it was reported that a population of 300,000 had been reduced to one-third owing to sleeping sickness, and the population of the

Buvuma Islands, Lake Victoria, which in 1900 was 56,000, in 1907 had fallen to 13,000. Great Britain had built a railway from Mombasa to the Lake shore and the disease was bidding fair to exterminate a people who, it had been hoped, would have a happy and prosperous future.

In 1891 the first human case seen in London was under the care of Stephen Mackenzie, and ten years later Manson saw two more patients who had come from the Congo and were admitted to Charing Cross Hospital. The same year three patients, also from the Congo, entered a hospital in Paris and were carefully studied. Two years before, Nepveu had seen trypanosomes in the blood of human beings, and in 1901 Forde saw them in the blood of a patient in the Gambia. That the protozoon played any part in causation, however, was not known at the time and we will postpone further consideration of it till we come to discussion of the ætiology of sleeping sickness.

To complete this part of the story mention may be made here of a lady from the West Coast who came under Manson's care in 1903 and died in England from sleeping sickness. In her blood the trypanosomes were found. This case is of importance because, though it was known that Europeans might harbour these protozoal parasites, it was a generally accepted idea that it was only natives who suffered from sleeping sickness.

2 FLY DISEASE OF CATTLE

Having sketched briefly the history of sleeping sickness, negro lethargy, to the beginning of the twentieth century, we will now go back a few years to consider another question—fly disease of cattle—which until the last years of the nineteenth century was not even suspected of having any connection with human disease. The two points, as it were poles apart, were advancing along converging lines to meet at the close of last century.

There is little doubt that the natives of certain parts of Africa have been aware for a long time, probably more than a century, of the ravages of the tsetse on their cattle, and explorers, if they had not received information from that source, very soon proved it by costly personal experience. Livingstone referred to it as long ago as 1849 as existing on the banks of the Zambesi and in his *Travels*, published in 1857, he mentions a "fly called Tsetse," *G. morsitans*, as abounding on the banks of the Zonga and states that the first specimen brought to England had been obtained by Major Vardon in 1848 on the banks of the Limpopo River. In writing of the fly he says

It is well known that the bite of this poisonous insect is certain death to the ox, horse and dog. In this journey we lost forty-three fine oxen by its bite. Harmless to man and wild animals and even calves so long as they continue to suck the cows. We never experienced the slightest injury from them ourselves personally, although we lived two months in their habitat. The south bank of the Chobi was infested by them, and the northern bank, where our cattle were placed, only fifty yards distant, contained not a single specimen. This was the more remarkable as we often saw natives carrying over raw meat to the opposite bank with many tsetse settled upon it.

Livingstone allowed them to bite him and to take their fill and he noted that a slight itching followed, but not more than after a mosquito bite. He describes the effects in cattle and the post-mortem appearances.

The poison-germ, contained in a bulb at the root of the proboscis, seems capable, although very minute in quantity, of reproducing itself, for the blood after death by tsetse is very small in quantity and scarcely stains the hands in dissection. The mule, ass and goat enjoy the same immunity as man and the game. Our children were frequently bitten, but suffered no harm and we saw around us numbers of zebras, buffaloes, pigs and antelopes feeding quietly in the very habitat of the tsetse undisturbed. [All this seems to support the view of Mense that sleeping sickness infection was not then present in East Africa and that it was introduced by members of Stanley's expedition.] There is not so much difference in the natures of the horse and zebra, the buffalo and ox, the sheep and antelope, as to afford any satisfactory explanation of the phenomenon. Major Vardon rode a horse up to a small hill infested by the insect without allowing him to graze [it was thought by some that the disease in cattle was due to a poisonous plant and not to the tsetse] and though he only remained long enough to take a view of the country and catch some specimens of tsetse on the animal, in ten days afterwards the horse was dead. A careless herdsman allowing a large number of cattle to wander into a tsetse district loses all except the calves. Inoculation does not secure immunity, as animals which have been slightly bitten in one year may perish by a greater number of bites in the next, but it is probable that with the increase of guns the game will perish and the tsetse deprived of food, may become extinct simultaneously with the larger animals.

The suggestion was made many years after to eradicate sleeping sickness by destroying the reservoir of the trypanosome—big game—but this would probably have led to more concentrated attack on man and greater prevalence of the human disease. In Livingstone's time, however, as we have seen, the bite of the fly was thought to be, and perhaps was, harmless for man.

"The tsetse," Livingstone goes on to say, "is a barrier to progress only till its well-defined habitat is known."

Further, Livingstone was acquainted with the fly which preyed upon the tsetse. Thus,

We have tsetse between Nameta and Sekhosi. An insect of prey, about an inch in length, long-legged and gaunt-looking, may be observed flying about and lighting upon the bare ground. It is a tiger in its way, for it springs upon tsetse and other flies, and, sucking out their blood, throws the bodies aside.

This was probably the Robber fly, *Asilidæ*. When he was about to leave the Valley of the Lekone a native brought to him a root which,

pounded and sprinkled over the oxen is believed to disgust the tsetse so that it flies off without sucking the blood. I deferred investigating it till I returned [but unfortunately no account is to be found later in his works]. It is probably but an evanescent remedy and capable of rendering the cattle safe during one night only.

Even so, if it fulfilled these expectations it would be valuable in passing through a short fly belt, also it might be active for a longer time, if application was repeated.

A picture of the tsetse appears on the title page of Livingstone's book, and others, on page 571 of the first edition, of natural size and enlarged and of the proboscis, drawn by Mr I. E. Gray of the British Museum from specimens obtained by Livingstone.

We see from the foregoing quotations that Livingstone ascribed the fatal effects to a venom injected by the tsetse when biting, others at a later period, among them Méguin (1875), Veth, Van der Wulp, Van Hasselt (1883), Schoch (1884), Railliet (1886), Laboulbène (1888) and Blanchard (1890) maintained that the insect mechanically transmitted some organism, just as any biting insect might inoculate anthrax.

Nothing further was known—no attempt seems to have been made to find out anything more—until 1894 when Sir David Bruce (then Major Bruce), having returned to England from Malta, met Sir Walter Hely-Hutchinson, Governor of Natal and Zululand. Owing to the latter's influence Bruce was sent out to Natal, *en route* to Ubombo in Zululand to investigate a condition called *nagana*, a very fatal disease of horses and cattle in certain parts of Africa. Curiously, as was thought at the time, the cattle could live and thrive on the barren hill of Ubombo but died when brought down to pasture on the grassy fertile plains. [Another account is that the Governor, a keen and enlightened administrator, arranged for an investigation, and Bruce, being in Natal at the time, was chosen to undertake it.] He found trypanosomes in the blood of infected cattle and, after carrying out some animal

experiments, concluded it to be the cause of nagana. This was a local name signifying 'depressed' or 'low spirited', in other parts it was called the 'fly disease' in the belief, afterwards proved to be correct, that the fly caused the sickness. Having reached this point, Major Bruce was sent away to Maritzburg to deal with an outbreak of enteric fever, but, through the persistence of Sir Walter Hely-Hutchinson, his studies were not interrupted for long and in 1895 he was back again at Ubombo. In the low-lying country between the sea and the higher ground on which the camp was situated was a so-called 'Fly-belt'. To test this, a native was directed to take a horse, in whose blood no trypanosomes were seen, from Ubombo to the plain and allow it to be bitten by the fly. This was done and in fifteen days the animal sickened and trypanosomes appeared in its blood. To confirm this and to find out more definitely what happened when an animal was 'fly-struck' natives were sent into this area with cattle and dogs, told to form a camp and let the animals be bitten by the tsetse. Soon after their return the same trypanosomal parasites were found in their blood. Having shown that taking healthy animals into a fly-belt and allowing them to be bitten was followed by appearance of trypanosomes in their blood, Bruce, to clinch the argument, to make assurance doubly sure that the flies and the flies only were the cause, and not the air, the water or the pasture of the plains, resolved, instead of taking the animals to the flies, to bring the flies to the animals in a place where the disease did not naturally occur, and he obtained the same result, thus showing that nagana and tsetse-fly disease were one and the same, and moreover, that the disease was not due to a venom injected, but to the transference of a parasitic protozoal infection (*Trypanosoma brucei*). He found that nearly all domestic animals—horse, donkey, cattle, dog—with the possible exception of the goat, were susceptible.

Trypanosome infection of lower animals has been known for almost a century, Valentine of Berne having seen it in the trout in 1841, the name was given by Gruby of Paris who found them in the frog. In 1878 Timothy Lewis described their presence in the blood of rats in India and in 1880 Griffith Evans saw them in the blood of horses and camels affected with surra and they cause the *mal de caderas*, a disease associated with staggering gait and weakness of legs, especially the hind legs, of horses, mules and dogs in South America, notably in Paraguay.

That they caused disease in cattle was not known for another fifteen years and it was this discovery made in 1895 that was to

prove of the utmost importance in solving the problem of human trypanosomiasis in Africa. We may mention here the fact that trypanosomes are also the cause of the condition known as *mbori* in dromedaries at Timbuctoo and of *soumaya* in horses and humped cattle at Ségun, propagated by *Tabanus dilænatus* and *T. biguttatus*, of El Debab which is very fatal to dromedaries in Algeria and is transmitted by *Atylotus nemoralis* and *A. tomentosus*.

Even now the problem was only half solved, namely, that the fly caused nagana or the trypanosomal infection of domestic animals, there remained for determination the question, Whence did the fly acquire the parasite? Bruce noticed and the natives corroborated, or possibly it was that Bruce followed up a hint from the natives, that fly-infested areas were also wild game areas, haunts of the buffalo, the wildebeeste, waterbuck and koodoo. Consequently, the blood of some of these was examined, but, at first at all events, the parasites were not found, they may have been too scanty to be revealed by examination of a few drops only. Inoculation of their blood into susceptible domestic animals, however, was followed by the finding of them. Also, it was observed that the tsetses lived and fed on the wild game. Later the parasites were found in buffalo and antelope although these were apparently in perfect health, in other words they constituted what subsequently were known as 'reservoir hosts'. The final link was forged when clean tsetse were allowed to feed on such wild game and then on domestic animals and the latter, after a period of incubation, fell sick with a fatal trypanosomiasis, whereas the effect of their feeding on the game animals caused no ill-effects in the latter. In short, Bruce's investigations demonstrated that nagana was a trypanosomal disease of domestic animals conveyed by *Glossina*, the tsetse fly, from wild game which acted as reservoir hosts.

Although at that time there was no thought of any connection with human disease, the matter was one of great economic importance because, in the first place, the animal disease was a scourge preventing successful agricultural undertakings in large and fertile districts of Africa, and secondly it was a serious obstacle to movement of cattle and of horses and necessitated slow, expensive and laborious travelling on foot with native portage.

3 LINKING UP OF THE HUMAN AND ANIMAL INFECTIONS

We have now come to the meeting-point of our two converging lines. The one, a human disease associated with the presence of

a trypanosome in the blood, and characterized by early enlargement of cervical lymph glands and, later, sleeping sickness, the other a trypanosomal infection of cattle with a high fatality rate

The first recognized human case was that of the master of a steamer on the Gambia River, an Englishman who in 1901 fell ill and was admitted to the Bathurst Hospital. As usual, the rise of temperature was ascribed to malaria, as in fact practically every febrile condition in every tropical and most subtropical countries has been at some time or other. The symptoms were, however, anomalous for malaria—irregular rashes of varied distribution, puffiness of ankles, tachypnoea, intermittent and irregular temperature not reacting to quinine. Dr Forde examined the patient's blood and found bodies "of a worm-like character" which he did not recognize. The man was sent to England and in 1902 entered the Royal Southern Hospital, at Liverpool, and was seen by Drs F M Sandwith and J E Dutton. His general state improved and the patient, when convalescent returned to West Africa. On the voyage he again became ill and on reaching the Gambia was again admitted to hospital at Bathurst. In December Dr Dutton again examined his blood and found the bodies already seen by Forde and recognized them as trypanosomes. The patient came back once more to England, but died soon afterwards, on New Year's Day, 1903.

The next development of the story was the finding in the blood of a native child in the Gambia the same protozoon, and Dutton in consequence named it *Trypanosoma gambiense*.

In 1902 the Liverpool School of Tropical Medicine decided to send an expedition to Senegambia to investigate the newly discovered condition more thoroughly. In the blood of the first thousand persons examined the trypanosome was found in seven, but the symptoms were slight and the morbid condition set up seemed to be a mild one in the native. At that time the connection with negro lethargy was not suspected.

Meanwhile, in 1901, a report had been received at the Foreign Office in London, telling of a widespread and disastrous epidemic of negro lethargy, sleeping sickness, occurring in Uganda. The first patients had been immigrants from Busoga and the report was that the disease was much more rife there than in Uganda. Dr Hodges, already mentioned as the newly appointed medical officer for Busoga, made an investigation and concluded that some 20,000 natives were already dead or were dying of the disease in his district. So important a despatch called for early action and the Foreign Office asked the Royal Society to send out a Com-

mission to investigate Aldo Castellani, Christy and G C Low were sent out and arrived at Kisumu in July 1902. The area affected by the sickness was found by Christy to be limited to a strip of land around the Lake shore and the islands on Lake Victoria Nyanza. Castellani was at Entebbe making post-mortem examinations and thought that the cause was a small streptococcus which he found in the blood (see later). He had also been examining the cerebrospinal fluid of patients in the late stages of sleeping sickness and in five out of fifteen of them he found trypanosomes, but without appreciating their significance.

Feeling that more light might be thrown by the aid of others who had been working in the country, the Royal Society asked the War Office for the services of David Bruce (now Colonel) of nagana fame. He, with Mrs Bruce (his able assistant in his previous work on undulant fever in Malta and in this and all his subsequent researches), Dr Nabarro and Staff-Sergeant Gibbons, arrived at Entebbe in 1903 and met Castellani who gave him his views concerning the streptococcus, but also mentioned, as incidental, his finding of trypanosomes in the spinal fluid.

Bruce, fresh from his nagana work, at once seized on this in preference to the streptococcus, he started looking for them and, together with Castellani, found them in the spinal fluid in 70 per cent of cases of sleeping sickness. They examined many healthy negroes and patients suffering from other diseases such as yaws, scabies, etc., and surgical conditions, but found no trypanosomes in them. Bruce gave all credit to Castellani, for he it was who with certainty observed them in the cerebrospinal fluid of sleeping-sickness patients, the credit for the recognition of their importance, however, must be given to Bruce.

The position at that time may be stated briefly thus. Trypanosomes are present in the cerebrospinal fluid of a large proportion, i.e. the majority of cases of sleeping sickness, and are not found in healthy natives or those suffering from conditions other than sleeping sickness. Trypanosomes might also be found in the blood of some patients but under these circumstances (and particularly if they were not present in the spinal fluid) the general health might not be seriously impaired.

Next, patients showing trypanosomes in the blood but not in the spinal fluid, were kept under observation, and it was found that, though they showed few or no symptoms at the time, they nevertheless later developed the well-known symptoms of sleeping sickness and died. After this it became the routine practice to examine both the blood and the cerebrospinal fluid, in 1904 gland

puncture was introduced and proved of great service in revealing trypanosomes in an earlier stage of illness

By this method of prolonged observation the members of the Commission were able to make valuable records of the clinical course of the disease. It might be acute or very chronic, the former more usual in Europeans, the latter in natives, but when once the trypanosomes appeared in the spinal fluid the course was usually—not invariably—rapid. Since lethargy did not occur in all cases, although the infection was essentially the same, a better name than sleeping sickness is *human trypanosomiasis*.

In speaking of the history of this disease, though clinical detail has no part in this respect, we should not omit the name of Kérandel, a doctor who in 1907 contracted the disease and described the symptom which bears his name—Kérandel's sign—and occurs early in the course. Fortunately, under continuous treatment, first with atoxyl and later with tartar emetic, he recovered. Europeans as a rule had a more hopeful prognosis in that they were usually seen early and their condition diagnosed in the earlier stages and they could be sent out of the country or at least away from the infected district. Natives, on the contrary, often did not come under treatment till a later stage, or if seen early and treated they would cease to attend when the chief symptoms cleared, they would return to their homes and very probably be bitten again by infected flies, the outlook, therefore, in their cases was mostly bad and many of them died.

The observers soon found that caution was necessary before pronouncing a person as 'cured' because they could not find the parasite in blood or spinal fluid, for intervals of improvement were not uncommon, and, though escaping recognition, the trypanosomes might still be present and the positive results from inoculation of the blood into animals (monkeys) showed that infection had not been eradicated. A fair working hypothesis came to be evolved by which if a patient had been under skilled observation for two years after cessation of treatment and had had for the whole time good health and freedom from fever and other symptoms, and if careful examination made at intervals failed to reveal trypanosomes, and repeated inoculation of the patient's blood into susceptible animals gave negative results, he might be regarded as cured, though even then there might be a mental reservation and academic doubt.

To return to the field studies of Bruce and the Commission. Their next step was to determine how the trypanosome infected man, what was the mode of infection, by what route did it pass

from the sick to the healthy. They noted the local geographical distribution of the disease—the old spot-map method usual in investigating outbreaks of disease—namely, the Lake shore, the Lake islands, and later the river banks, and they heard from the natives that if cases were notified from the interior these had come from known infected areas, there being steady communication between the shore districts and the interior, and that infection did not spread in the interior. They remembered also the reports of long ago of negro lethargy in the slaves in the West Indies (ascribed there to home sickness, brooding and nostalgia) although patients so affected did not pass the disease to others. They heard also that the natives of French Guinea ascribed the disease to a fly which propagated infection by its bite. Bruce called to mind also his nagana investigations and the transmission of trypanosomes by *Glossina*. In this way suspicion was turned on the tsetse, and the local European missionaries, headmen and others were questioned as to the existence of tsetse in the districts—the Lake-shore islands—where sleeping sickness prevailed. The reply was that it did not exist there, but that *kiva* was very common. On examination, *kiva* was found to be the local name of tsetse. Bruce called in the missionaries and others to his aid, persuading them to catch the *kiva* and note where in their respective districts it was found, whether in marsh lands or plantation bush, forest or open country and Lake shore, also whether it was a day-, noon-, or night-biter, what animals it bit, and finally whether cases of negro lethargy occurred in the areas where the fly abounded.

They were infused with his enthusiasm and responded so well that within three months he had received 460 collections of biting flies and another spot-map was made plotting the localities where these had been captured. Comparing this map with that of the prevalence of cases of the disease he found that they coincided, that the fly lived and thrived in forest and dense undergrowth on the shores of lakes, on the Lake islands and along the rivers where also the natives were accustomed to meet for palaver and trading. The theory was now ripe for crucial tests. *Kiva*, tsetse, *Glossina palpalis*, were allowed to feed on a sleeping-sickness patient and after varying intervals were permitted to bite monkeys, the latter subsequently were found to harbour trypanosomes in their blood. Again at that time natives in large numbers were coming to Entebbe to work for Government for a month in lieu of paying a hut tax. Flies caught in their huts were brought to the laboratory and allowed to feed on healthy monkeys, which after an interval were found to have blood trypanosomes. The

Gazette of 1873) who called attention to this glandular enlargement and thought that the train of symptoms resulted from their pressing on the vessels going to the brain and reducing the cerebral blood-supply Gore, however, shows doubt, for he says that the glands may be quite small, and but slightly enlarged, and also that scrofula is common among the natives and he suggests alternatively that negro lethargy may be due to cerebral sclerosis and tuberculosis He adds, however, that the matter is by no means clear and calls for further observation Corré in 1876 (see p 457) had noted the cervical adenitis

5 Other theories may be mentioned as having a transient vogue, such as that the disease was a peculiar kind of malaria, or, later, was due to hookworm infestation Patients heavily infested by these helminths are anæmic, dull, and slow, mentally and physically, but this disease is common where sleeping sickness is non-existent Cagigal and Lepiérn ascribed it to a bacillus, Marchoux to Frankel's diplococcus (*Pneumococcus*) and we now come to more scientific ground

Bacteria as Causative

Apart from Marchoux's suggestion that Frankel's organism might be causative, Broeden also thought a diplococcus or streptococcus was responsible We do not know whether this was the same as that seen by Dr (now Sir Aldo) Castellani in the cerebrospinal fluid in 1903 and shown by him to Dr Cook Castellani, as we have stated, also saw trypanosomes in the spinal fluid but did not connect them ætiologically with the disease Dutton and Todd, two years later, showed that a diplostreptococcus was a fairly frequent finding at autopsy and they looked upon it merely as a subterminal invader Castellani at first believed this organism to be the cause of sleeping sickness, but later came to the same conclusion as Dutton and Todd—that the streptococcal infection was a concomitant of the late stages, but played no part in the causation

The *Filaria* as cause In the first edition of Manson's *Manual of Tropical Diseases*, published in 1898, *Filaria perstans* is postulated as the cause of negro lethargy, but the statement is made with Manson's characteristic caution He says he has found the microfilaria in cases of the disease, but that it is present, and even in large numbers, in a considerable proportion of negroes, further, that if it is the cause, he is unable to conjecture its mode of action, unless perhaps it be by blocking vessels and interfering with the circulation of the brain In the blood of two sleeping-sickness patients from the Congo seen by Sir Patrick Manson in

1898 he found the filarial embryos and concluded apparently that he had determined the cause, forgetting that the native is a pluralist as a harbourer of parasites and that malaria, filaria, trypanosomes, amœbæ and helminths of several species may all be found in the same subject. In the *Journal of Tropical Medicine* for 1898 these two patients from the Congo who had been admitted into Charing Cross Hospital are described in detail and from a study of them Manson put forward as a working hypothesis that (1) The germ of sleeping sickness operates primarily on the encephalon, (2) This germ is possibly *Filaria perstans*, (3) The parasite in its wanderings, either by entering the brain or interfering more or less directly with its nutrition, may bring about a cessation of its function, ultimately leading to secondary neuro-muscular malnutrition and symptoms of sleeping sickness.

Dr Christy, a member of the Royal Society's Commission of 1902, found that although the sleeping-sickness area was limited to the islands and the Lake shore of Victoria Nyanza and that many of the patients harboured *F. perstans*, this latter infection was more widespread and did not correspond with the sleeping-sickness area, that is, sleeping sickness and *perstans* infection were not always coexistent. For a time, however, evidence in its favour seemed to be accumulating, thus J H Cook in the same journal, in 1901, describes the disease in Uganda whereas up to that time it had been regarded as a West African disease. He also notes the presence of *Microfilaria perstans*. Sims the same year saw cases near Stanley Pool, on the Congo, and Manson found the parasites in blood-films sent from various parts of the Congo Basin. The interpretation was that "the disease with *F. perstans* has crossed the watershed between the Congo and the Nile and arrived at the upper reaches of the Nile. It may now spread along the Nile and rapidly with opening up of trade routes." The following year it had extended along the shores of the Victoria Nyanza and into Uganda, in many districts it was reported that half the population was attacked and that all those attacked died. The association of sleeping sickness and *Filaria perstans* seemed to be very close, it was reported that neither was seen until both appeared together, in 1900, and *Mf. perstans* had not been seen in the blood of members of the Baganda tribe until 1901 when sleeping sickness appeared in epidemic form.

Trypanosomes

When Forde first saw trypanosomes in the blood of a patient in the Gambia in 1901 considerable interest was aroused in what

was thought to be a "newly discovered disease in man," and in a specimen of the blood sent to the Liverpool School of Tropical Medicine J E Dutton, on 1st August, 1902, recognized it as a trypanosome Dutton also found "the worm" in the blood of a native Gambian child of three years, showing no symptoms of disease clinically When C W Daniels saw them in Manson's patient the same year and later in another patient in Africa, it was presumed that the disease was more widespread than had been believed and the speculation was indulged that "some of the anomalous chronic fevers in man, such as kala azar, which have hitherto defied classification, may, on investigation, prove to be due to trypanosomes in the blood"

When Bruce and Nabarro arrived at Entebbe in 1903, Castellani told them of the streptococcus which he had found and also mentioned, though he did not apparently lay stress on this as a possible causative agent, that he had seen trypanosomes in the cerebrospinal fluid of sleeping-sickness patients Bruce, as we have mentioned above, seized on this Castellani reported finding them in five out of fifteen cases of the disease and Bruce, Castellani, and Nabarro together found them in the fluid of 70 per cent of (thirty-four) cases Bruce gave the credit to Castellani, for he had certainly been the first to see them in these cases, without, it would appear, recognizing their ætiological significance Examination of natives suffering from other diseases and surgical conditions did not reveal them Sir A R Cook, writing in the *East African Medical Journal* in 1936, states that Chalmers had called the group Castellanela, and Dutton's *Trypanosoma gambiense* Castellanela castellani The former name has, however, priority and has been retained although Castellani thought that those discovered by him differed from Dutton's and called it *T ugandense*, later the two were shown to be identical [In a recent Italian work on tropical medicine by Castellani and Jacono, the name Castellanela is used for the genus *Trypanosoma*] In Castellani's original paper, communicated by the Malaria Committee of the Royal Society on 14th May, 1903 (*Proc Roy Soc*, Vol 71, pp 501-8), he states

Trypanosoma fever is by no means uncommon among the natives in Uganda these cases bear no resemblance in their clinical features to sleeping sickness

The trypanosoma found in the cerebrospinal fluid of sleeping sickness does not as far as I have been able to make out differ materially in size and shape from the species one finds in the blood of trypanosoma fever, *Trypanosoma gambiense* (Dutton), but possibly it is to be differentiated from this one because in it, as a rule, the micro-nucleus lies

nearer the extremity and the vacuole is apparently larger Besides, its movements are not apparently so active, but this fact might be due to the effects of the centrifuge In case it should prove to be a new species, the trypanosoma I have described might be called from the country where I have found it first—*Trypanosoma Ugandense*

The controversy regarding the honour of priority in recognizing the ætiological rôle of the trypanosome in sleeping sickness was carried on in both medical and lay papers, and personal recriminations were not excluded from what should have been a purely scientific discussion, the spectacle was neither very edifying nor seemly We have stated the facts and represented the position to the best of our ability In conclusion we may quote the two final paragraphs of Castellani's paper and the remark of Sir Michael Foster, Secretary of the Royal Society at the time

At the post-mortem examination of 80 per cent of the cases where I found during life the trypanosoma, I grew from the blood of the heart and from the liquid of the lateral ventricles the variety of streptococcus I described many months ago in my first note Up to that time I had never found the trypanosoma, but this is easily explained by the fact that I did not use the technique I have described in this note, viz, examination of a large quantity of the liquid after long use of the centrifuge

Influenced by my last investigations I would suggest as a working hypothesis on which to base further investigation that sleeping sickness is due to the species of trypanosoma I have found in the cerebro-spinal fluid of the patients in this disease, and that at least in the last stages there is a concomitant streptococcus infection which plays a certain part in the course of the disease

The Secretary's note follows

As so far supporting the observations by Dr Castellani recorded in the above communication, it may be desirable to state that Colonel Bruce, to whom in Uganda Dr Castellani made known his discovery of the Trypanosoma, and who is now continuing the investigation begun by Dr Castellani, has sent to the Royal Society a telegram, received May 4th, stating that since Dr Castellani left, in thirty-eight cases of sleeping sickness, he had found trypanosoma in every case in fluid obtained by lumbar puncture, and that he had found trypanosoma in the blood in twelve out of thirteen cases of sleeping sickness

MICHAEL FOSTER

Profiting by his studies and discoveries on nagana Bruce showed that the tsetse fly, *Glossina palpalis*, was the carrier, or the vector of the trypanosome and summarized the knowledge of the time on human trypanosomiasis and its relation to sleeping sickness in the following propositions

1 The trypanosome—*T gambiense* of Dutton—found in the blood of natives in West Africa, the Congo, and Uganda, is identical with that found in cases of sleeping sickness

2 Trypanosomiasis (Trypanosome fever) is only the first stage of the disease

3 Europeans as well as natives are susceptible, there is no racial immunity

4 The disease is eventually fatal

5 There is no real evidence that any of the lower animals take any part in the spread of the disease

6 It is conveyed from the sick to the healthy by tsetse flies (*Glossina palpalis*) In Uganda the distribution of the fly and of the disease is the same, where there is no tsetse sleeping sickness is absent

7 There is a certain amount of evidence that species of tsetse other than *G. palpalis* can convey the disease, therefore if infection is introduced into a healthy part of Africa the local species would probably be able to transmit it

8 The weight of evidence is against transmission of infection by other biting flies

9 There is no proof of any developmental stage in the tsetse, transference is mechanical This was based on two observations (a) That the fly remains infective for forty-eight hours only, (b) That, if development took place in the fly one would not expect it to be infective for some time after it had sucked the blood of a patient (compare malaria with ten and yellow fever with twelve days' interval)

10 All stages of development of *Trypanosoma gambiense* take place in man, a second host is therefore not necessary for completing its life-cycle

11 To prevent spread of the disease the main points to be considered are (a) Checking the movements of infected natives into healthy, i.e. non-infested areas, (b) Prohibiting immigration of healthy natives into infected areas, (c) Evacuation of areas [this would seem to contradict (a) above], (d) Destruction of flies and their breeding places

Most of these propositions are as valid to-day as when Bruce stated them, but some have had to be modified Thus (4), "the disease is eventually fatal" applies only if it remains untreated, also, as regards (5), game and wild animals have been shown to be reservoir hosts, again (9) and (10), though mechanical transmission is possible within a short time of the infective feed the usual mode is cyclical transmission after a period of development of two to three weeks in the tsetse fly

In 1903 cultivation of trypanosomes was demonstrated

by the use of the Nicolle, Novy and MacNeal (N N N) medium

One or more Trypanosomes concerned in causing Sleeping Sickness

The problem of causation was now believed to have been solved. *Trypanosoma gambiense* was the cause, the sole cause, of the disease. Thomas and Breinl (in Memoir XV of the Liverpool School of Tropical Medicine) discuss the question and describe in detail the pathology of sleeping sickness. They conclude that the trypanosomes of sleeping sickness from various localities are one and the same, *T. gambiense*, and so far as the distribution of the disease was known at that time (1905) they were probably correct. They noted the plasma cells and small-celled infiltration of the vessels of the brain and cord, hæmorrhage of the lymphatic glands, necrotic areas in the spleen, and degenerative changes in the bone-marrow.

In 1910, however, J. W. W. Stephens and H. B. Fantham had under observation a European who had become infected in the Luangwa Valley, Rhodesia. They found a trypanosome which appeared to differ from *T. gambiense*. This was reported to the Advisory Committee of the Tropical Diseases Research Fund and a paper on it was read before the Royal Society. They gave as their reasons for regarding it as a different species, mainly the shorter form with posteriorly situated nucleus, and they proposed the name *Trypanosoma rhodesiense*. In the Luangwa Valley *Glossina palpalis* was not found and Bruce, summing up the position in 1911 (in a paper in the *British Medical Journal*) repeated in the main what he had found before (see p. 473) adding that probably wild game was the reservoir and that *G. palpalis* was the only carrier in nature, though *G. morsitans* and *G. pallidipes* were under suspicion. Up to this time transmission was thought to be mechanically, but doubts were creeping in (see later).

Next year, Allan Kinghorn and Warrington Yorke showed that the transmitting insect was *G. morsitans*. Further study revealed that this new form of sleeping sickness occurred in Nyasaland as well as in Rhodesia and that it ran a more rapid course than the Uganda type. Between 1911 and 1914 Bruce, who was then over sixty years of age, found that the vector, *G. morsitans*, lived not only on shores of lakes and banks of rivers, as did *G. palpalis*, but also inland. It was not only on the morphological differences between the trypanosomes, therefore, that the varieties were distinguished but on the clinical differences in the illness to which they gave rise and the difference of vector. By this time

several trypanosomes had been described as occurring in Africa, in man and animals, and now *Trypanosoma grayi*, not infrequently found in tsetse, was traced to crocodiles, and one writer in 1911 was expressing the general opinion when he said "it will be some years before anything like order is evoked out of the chaos of specific names" We shall see when we come to relate recent work that the tangle has not even yet been unravelled

During the next two or three years evidence was accumulating that *T. gambiense* and *T. rhodesiense* were distinct, the main point now being the posteriorly situated nucleus in the latter C M Wenyon, however, pointed out that this alone was not a sure criterion, he found a similar posterior nucleus in *T. pecaudi* and at the same time noted that some workers regarded *T. pecaudi* and *T. brucei* as one Bruce, Harvey, Hamerton and Lady Bruce studied intensively the 'new' trypanosome and found that the percentage with a posterior nucleus varied and they came to the conclusion that evidence was accumulating to show the close similarity, it might be identity, of *T. rhodesiense* and *T. brucei* Re-examination of nagana strains from the place where Bruce first discovered them furnished additional support—in fact they decided that the new human trypanosomiasis of Nyasaland was nagana in man They found, further, that it was present in the blood of many wild game and they regarded the latter, therefore, as a menace to man and suggested their destruction—extermination even—as a preventive measure

The following year, 1914, J W Scott Macfie obtained a strain of trypanosome from a sleeping-sickness patient in Southern Nigeria which appeared to be less virulent for laboratory animals than Yorke's strain and which he believed to be of yet another species, he named it *T. nigeriense* He found it in the Eket district The natives stated that the disease had existed there for a long time but that it had lately become more prevalent During a period of sixteen months the protozoon was found in 222 cases, chiefly by means of gland puncture (see later) or examination of excised glands The clinical course was milder than had been observed in *rhodesiense* infections and during the time of the investigation only nine had ended fatally Enlargement of glands was a well-recognized characteristic and the natives were accustomed to excise them *Glossina palpalis* was rare in this district, the commonest tsetse was *G. tachinoides* It was thought, therefore, that the infection in this part of Nigeria was a mild type due to *T. nigeriense* and transmitted by *G. tachinoides*

Modern research has proved that mildness of course does not imply difference of species of trypanosome W E Cooke, A L Gregg, and P H Manson-Bahr in a paper published in 1937 drew attention to avirulent strains of *T gambiense* recorded from Northern parts of West Africa Three cases are detailed which would not have been detected had not routine examination of the blood of all patients from West Africa been the rule One expressed himself as feeling quite well and showed no clinical symptoms, the other two had had fever on the Coast, presented the local reaction—the trypanosome chancre of Graf—and the blood infection was in each case a heavy one Five years before Manson-Bahr had noted that the virulence of strains of the same trypanosome for Europeans in the Gold Coast was diminishing Similar findings have been recorded elsewhere Mild strains of *T rhodesiense* have been reported by French observers in Europeans in the Ivory Coast, by van den Branden in the Belgian Congo and by Lamborn and Howat in Nyasaland This was not a new idea, thirty years ago, in 1908, Davey mentioned avirulent strains of the same trypanosome

In 1915 Sir David Bruce delivered the Croonian Lectures, which by systematizing the facts discovered up to that time did much to clarify knowledge of the subject and to evoke order out of the chaos of specific names for the various trypanosomes He did this by classifying them in three well-defined groups, giving their geographical distribution and describing the characters and habits of *Glossina*

I *The TRYPANOSOMA BRUCEI group*

- (1) *T brucei* and *T gambiense*, pathogenic for man
- (2) *T evansi*, the cause of surra in horses in India and eastern Asia
- (3) *T equiperdum*, causing dourine in horses in northern Africa and parts of Europe

II *The TRYPANOSOMA PECORUM group*

- (1) *T pecorum*, in horses, donkeys, oxen, sheep, goats and pigs, spread by *Tabanidæ* and tsetse In *Glossina morsitans* development occurs in the intestine and forward to the salivary duct or hypopharynx, but not to the salivary gland
- (2) *T simia*, occurring in monkeys and in pigs and warthogs

III *The TRYPANOSOMA VIVAX group* Contains four species affecting horses, cattle, sheep and goats The develop-

mental stages in *G morsitans* at first occur in the labial cavity of the proboscis, more in the intestine, later the hypopharynx is infected

The first only of these groups and the first subsection of it concern us now

In 1911, when Bruce went to Nyasaland on the Royal Society's Commission he found a trypanosome in wild animals and showed that morphologically *T rhodesiense* was indistinguishable from the *T brucei* he had previously discovered, he found that 32 per cent of wild animals which he examined were harbouring it (as a reservoir) and that one in 500 wild tsetse flies carried the infection. The Nyasaland type of sleeping sickness was more severe and more fatal than the northern *gambiense* type and he inferred that this, Nyasaland, form of the disease might occur wherever *T brucei* was met with in the animals, most of Central Africa, in fact

Acting on this belief of the identity of *T rhodesiense* and *T brucei*, Bruce, Kinghorn and Warrington Yorke in 1915 recommended destruction of big game as a preventative of human infection, but C Christy, three years later, when discussing 'fly-belts,' records great seasonal variation in the prevalence of tsetse in the fly areas of Africa. Of 160 wild animals which he shot he found three only infected with "trypanosomes of possibly human types" and he doubts, therefore, whether extermination of game, even if it could be accomplished, would stop infection of man. More effectual would it be to destroy vegetation and so prevent the flies breeding

In 1919 Taute and Huber showed that *G morsitans*, after feeding on animals harbouring *T brucei*, did not infect man by their bite and further 129 negroes and two Europeans inoculated directly with blood containing *T brucei* did not develop symptoms, nor did trypanosomes appear in their blood, though animals could readily be infected with the same blood. This is strong evidence against identity, moreover *T brucei* has a much wider distribution in wild animals than has *T rhodesiense* in man

A piece of evidence which may be regarded as favouring the identity was an outbreak in the Mwanza area of Tanganyika Territory to the south of Lake Victoria Nyanza, which was attributed by H L Duke and C F M Swynnerton indirectly to decrease in the game whereby man was more attacked. The transmitter was found to be a new species of tsetse, *G swynnertoni*, which would follow natives for a mile or so and would cross an open space of some seventy yards. These facts had an important

bearing when, later, preventive measures of clearing round populated areas near forests came to be considered

The confusion was not made any less when Kleine expressed his opinion that *T gambiense* and *T rhodesiense* were one, though strains might vary in their virulence. The morphological distinctions which had been relied upon he found not to be valid, since *T gambiense* might also show forms with posterior nucleus.

The question of identity or not of these trypanosomes has been a vexed one for several years—nearly a quarter of a century—particularly whether *T rhodesiense* infection was derived from the *T brucei* of cattle disease and of healthy antelopes. More recently the evidence against seems to be accumulating. The experiments of Taute and Huber who failed in 1919 to infect man by direct inoculation of blood from animals with *T brucei*, or indirectly by tsetse, *G morsitans*, which had fed on the latter, have been already referred to above. Kleine also failed to infect human volunteers with the animal trypanosomes and as recently as 1933, Dr J F Corson, a keen and intrepid investigator, made the experiment upon himself with negative results and in the following year H L Duke obtained the like results from attempts at cyclic transmission.

On the other hand some authorities with long and extensive experience believe that *T brucei*, *T rhodesiense* and *T gambiense* are merely varieties of the same parasite. They are convinced that when man is exposed to infection by bites of the game-tsetse which is carrying *T brucei*, he is liable to infection and the trypanosome may establish itself in either a mild or virulent form, the latter as *T rhodesiense*, hence they veer again to the opinion of Bruce, Kinghorn and Yorke expressed in 1915 that when human settlement was contemplated in a place where game-tsetse abounded the game in the vicinity should be sacrificed.

Duke, whose experience with trypanosomes is wide and long, came to the conclusion that *T brucei* was the same species as *T rhodesiense*, the latter name being given to those strains of *T brucei* which utilize man as host. He believed that much of the mortality in cattle which was ascribed to *T brucei* was in reality due to *T congolense*. The following has been offered in explanation of this. Bruce when studying nagana thought (it is supposed) that the trypanosomes of the ox, horse, donkey and dog were one and the same. He sent one infected dog to England and Plimmer and Bradford named the parasite *T brucei*. This strain is now known to be very pathogenic for equines and canines, but not for cattle.

As sleeping sickness associated with *T. rhodesiense* came to be more systematically studied its area of distribution was discovered to be much more widespread than had been believed, and to include East Africa from north-eastern Rhodesia, Nyasaland, Portuguese East Africa and Tanganyika to Lake Victoria Nyanza and southern Egyptian Sudan. It is thought that introduction into Nyasaland took place from Tanganyika in 1908 or after, for in that and the preceding year no cases were found among 60,000 natives examined, but by 1915 the disease had spread widely. In Ruanda-Urundi, lying north-east of Lake Tanganyika, 87 per cent were found infected when examination by gland puncture was carried out.

In Kenya Colony J. O. Bevan discovered several centres existing about Lake Victoria Nyanza, in some the morbidity rate was high, up to 53 per cent, the preponderance being greatest among the children and younger people who spent much time fishing in the rivers.

We have stated above that infection might be in a mild or virulent form and that change in virulence does occur, as exemplified by the experience of workers in Nigeria. They found there a mild form of *T. gambiense* infection persisting over a large area and affecting from 3 to 5 per cent of the inhabitants. At certain times, and without any discovered cause an outbreak with high fatality rate might suddenly arise. Explanations offered, which were largely hypothetical, were that movement of natives might introduce new strains, or that strains setting up a mild form of infection might be transmuted into virulent strains. During 1935 more than 80,000 cases were found among the natives, in many the disease was mild, but over an increasing area it was becoming steadily more virulent in type. In three areas *G. palpalis* and *G. tachinoides* were found and bordering on these an area in which *G. morsitans* was present.

The position, though certain details have been studied more intensively, remains much the same as when we wrote in 1929.

There is room for research upon the relations of the human and animal trypanosomes. On the one hand Kleine holds that *T. rhodesiense* represents the form taken by *T. gambiense* when introduced into a new area and transmitted by tsetse flies of the *G. morsitans* group, and that it is distinct from *T. brucei*, whereas Duke regards *T. rhodesiense* and *T. brucei* as the same, and Lavier that *T. gambiense*, *T. rhodesiense* and *T. brucei* are one species. Wenyon and Fletcher state that if *T. rhodesiense* is identical with *T. brucei* it can be but rarely that man becomes infected by *G. morsitans* which has itself contracted the parasite from animals. Such inoculation of *T. brucei* is, however, possible.

and would account for the occasional appearance of infection of the *rhodesiense* type in places such as the Sudan. Then, having gained a footing in man it might set up an outbreak by *G. morsitans* conveying infection from man to man. Whatever the actual relationship, *T. rhodesiense* certainly gives rise to more acute infections in man and experimental animals than does *T. gambiense*, responds differently to drugs and is transmitted by flies of the *morsitans* group instead of the *palpalis*. Moreover, game seem to take but little part in the spread of *T. gambiense*, while the relationship of game to the spread of *T. rhodesiense* is not known. Dye's investigations appeared to show that the extension was traceable, in many cases which he followed up, from man to man and that game could be excluded from three at least.

It will be fitting here to say a few words on the cultivation of trypanosomes pathogenic to man. We distinguish 'cultivation' from 'keeping alive,' the latter being spoken of later when we discuss the historical aspect of treatment and testing the effects of drugs. Cultivation is of interest not merely from the intrinsic fact of its accomplishment being of historical importance, but scientifically in revealing the stages through which the trypanosome passes, the changes which it undergoes under these conditions and indicative of what may be expected to occur in natural development.

In this respect one of the most important is that described by Andreas von Razgha in *Zeitschr. f. Parasitenkunde*, in June 1929. In his first experiments Razgha utilized the hypotonic medium of Ponselle, devised in 1924. Details of this will be found in the article referred to, all that need be said here is that the peculiar physico-chemical character of this medium is evidenced by the fact that on addition of blood the corpuscles very speedily sink to the bottom.

Razgha added blood containing trypanosomes to this medium, left the tubes in the dark for a fortnight and examined them but saw no trypanosomes. In the tubes was found a fine fibrin network, at times a distinct blood clot, so he decided not to inoculate the extracted blood directly into the tubes but to dilute it with Ringer's solution, centrifuge, and add the supernatant fluid, which contained the trypanosomes, to the medium. Still no trypanosomes were found after an interval for growth. He then again examined the tubes which contained the remainder of the fluid, after part of the supernatant had been added to the culture tubes, i.e. the rest of the supernatant and the residual deposit which he had kept as controls. To his surprise, although the tubes first examined revealed no trypanosomes, these latter contained them in large numbers. Further study showed that only certain sera

would permit of this growth—those of man or monkey—while those of rabbit, rat, goat and other laboratory animals would not. The medium which gave such good results with *T. gambiense* consisted of equal parts of Ringer's solution (with 0.6 per cent NaCl) and of citrated human blood, each tube containing 2–3 c.c. Out of forty attempts cultivation succeeded in thirty-one. In one, living flagellates were found up to the forty-fourth day, when the tubes were kept at 22–24° C. During the first two days the trypanosomes decreased rapidly and many degeneration forms were seen, some, however, survived and divisional, cultural, forms appeared during the next two days and thereafter blood forms became fewer and cultural forms more numerous and rosettes were seen between the third and sixth days. At the end of a week a highly refractile granule appeared at the junction of the middle and posterior thirds of the body of the trypanosome—probably the blepharoplast vacuole. Gradually the body became stuffed with granules. Long, narrow forms of trypanosome showed a marked resemblance to those found in the gut of *Glossina*, but typical crithidia were not seen. First subcultures gave rise to similar process of growth, but further attempts at subculture did not succeed.

Also, success was attained with *new* strains, not with old strains maintained by animal passage. Razgha believes that the failure of previous attempts at culture was due to the use of old strains, possibly because of a gradually developed susceptibility to human serum or because long sojourn in the animal host had changed the parasite so that it would no longer develop in the human host or culture tube.

This last has been borne out by more recent cultivation experiments, when Reichenow showed that old laboratory strains were cultivated much less easily than strains recently isolated, and P. Brutsaert and C. Heuvarde found that non-transmissible strains could not be cultivated, the reverse of this did not always hold good, they were unable to cultivate strains which were readily transmissible by tsetse.

Brutsaert and Heuvarde made use of five different media: (1) Citrated human blood and Ringer's solution containing 0.6 per cent NaCl in equal parts. (2) Citrated human blood and Locke's solution in equal parts. (3) The same as the first with cholesterol, 0.5 gm per litre. (4) The first *plus* 10 gm of Witte's peptone and the same weight of Criguet's (gold medal) gelatin. (5) Citrated human blood and Tyrode's solution.

Their experiments were made with six strains of *T. gambiense*,

one of *T. brucei* and three of *T. congolense*. One of the *gambrense* strains was carried through forty-nine subcultures in 428 days, one of the *congolense* through thirty-six subcultures in 339 days, and the *brucei* through twenty-four subcultures in 206 days. The best medium proved to be citrated human blood and Ringer's solution with the cholesterol (No. 3 above), next to this came the blood and Ringer without cholesterol, and the blood and Tyrode's solution (Nos. 1 and 5). That pathogenicity for animals was not lost by cultivation is evidenced by the fact that two goats were infected with *T. congolense* after 156 days of culture.

5 DIAGNOSIS

We have seen above (p. 480) that the disease caused by trypanosome infection may vary greatly in severity, from one so mild that the patient presents no clinical symptoms and the case would have been overlooked if blood examination were not systematically carried out as a routine, to one so severe that death results in a few months. This leads us naturally to the question of method of diagnosis, a question of historical as well as clinical interest.

At the beginning of the present century 'in the days of Bruce,' of Nabarro and of Castellani, diagnosis was made in the earlier stages of the disease by examining samples of the peripheral blood for the presence of trypanosomes, in the later stages by examination of the cerebrospinal fluid. Afterwards, when their presence was suspected but, being few, they escaped recognition in direct smears, inoculation of the blood into susceptible animals was a method employed as a subsidiary to this.

Within a year or so, in fact, as enlargement of the cervical glands was recognized to be an early symptom, Dutton and Todd (as mentioned in Memoir No. XV of the Liverpool School of Tropical Medicine already referred to) advocated gland puncture and examination of the extracted gland juice for the protozoon, and the value of this method was confirmed by Greig and Gray (*Report of the Royal Society's Sleeping Sickness Commission, No. VI*).

These remained the chief, one might say the only, laboratory methods of diagnosis for the next quarter of a century, then methods which had been found useful in other diseases—leptospirosis, kala azar, for example—were applied to sleeping sickness and recommended by certain investigators as of diagnostic value in this. Three of these may be mentioned, the formol gel, agglutination tests and the adhesion phenomenon.

There is no need to give details of the *formol gel* test, they are common knowledge. Seeing that a positive result is given in other diseases the test is qualitatively of little if any value, but Ledentu and Vaucel, of the Pasteur Institute, Brazzaville, made an intensive study of the test and found it useful when attention was paid to the *reaction time*. They reported that in the early stages of untreated cases the reaction is a rapid one, a gel being formed in seven minutes, in the second stage it is three to four times as slow, twenty-five minutes in patients whose spinal fluid contains trypanosomes, in others, also in this stage, with changes in the spinal fluid, though trypanosomes were so scanty as to escape detection, the reaction was not complete for two hours. Treatment, they observed, retarded the reaction and might even negative it. One would think, therefore, that a series of tests carried out at intervals would be of prognostic value, but this, they stated, was not the case.

Auto-agglutination of erythrocytes was a phenomenon reported by some investigators to run parallel with the formol gel test, marked auto-agglutination and rapid formol gel reaction going hand in hand as indicative of trypanosome infection, negative formol gel and absence of auto-agglutination excluding it.

The *adhesion phenomenon*, described (though not originally devised) by Davis and Brown in 1927, is one of wide application. They found that the 'opsonin-like substance' in the serum responsible for the reaction is thermostable and can withstand a temperature of 65° C for two hours. They demonstrated the reaction to be specific with sera of animals immunized against leptospiræ, *T. equiperdum*, *T. lewisi* and *T. rhodesiense*, and can be adopted, therefore, for diagnostic purposes. Its use was extended to the study of the relationship of game to the trypanosome infections of domestic stock and of man, and to the demonstration of latent infections in the former, infections which may be very difficult to locate but which may fulminate when the animals are exposed to adverse conditions. It is not of such service as other tests for the diagnosis of early cases, but in the later stages, which are the commonest by the time the native comes under observation, it is of real value, a high percentage of positive results being obtained in the second and third periods, even when trypanosomes cannot be found microscopically. Suspected cases which do not react to the test should be given a short course of treatment and then retested, when the result will often prove to be positive.

The question of clinical diagnosis we are not further concerned with, as this is not of historical interest, though reference will

be made to it in the section dealing with distribution of the disease, for erroneous diagnoses were made and sleeping sickness reported to be present in places where further investigation showed that it did not exist, as, for example, kgotsella in Bechuanaland

6 DISTRIBUTION OF SLEEPING SICKNESS

There is no doubt that the present distribution of sleeping sickness is very different from what it was in the early days of its discovery. It is not that further knowledge and more thorough examination have revealed the existence of the disease in places where it prevailed unrecognized, its area has extended widely and its distribution and severity have varied from time to time. We have already noted the fact that Livingstone, though he knew the danger of tsetse for cattle and horses, would watch with interest the flies bite himself and had no fear. Probably in his day East Africa was free from the human disease. We have pointed out also the unwitting importation of infection by Stanley's column marching to the relief of Emin Pasha. Sir Harry Johnston remarks in his book, *The Opening Up of Africa*

Opening up of the Continent has carried the terrible sleeping sickness from one or two patches of Congoland over much of Uganda, German East Africa and British Central Africa. Similar diseases have swept away the greater part of a Colony's supply of cattle and horses

In Nigeria trypanosomiasis was fairly general, and, as we have written elsewhere, were the tsetse absent the expansion of the cattle industry in this country would be almost unlimited. Horses, cattle, sheep, pigs and goats are numerous in Southern Nigeria and, though small, they appear to thrive in these fly-infested areas and to be tolerant, to a large degree, of the trypanosomes which are present in their blood. We do not know for certain whether these cattle are immune (that is, non-infectable) or resistant and tolerant. If resistant whether this property is transmissible or the result of repeated exposure

We have mentioned already (p. 480) the remarkable change which has occurred in the virulence of human trypanosomiasis in Nigeria

Survey of trypanosomiasis in the Gold Coast in 1925 showed several species of tsetse to exist there and that their prevalence varied from season to season, depending, at least in part, on the rise and fall of the Volta. *Congolense* and *vivax* infections were common, but human disease was rare. Only thirty-seven cases, five deaths, were recorded in that year and in 1926 sixty-seven cases and eleven deaths, the larger number being ascribed, not to

increase in prevalence of the disease, but to the natives presenting themselves more readily for treatment as this became more widely known. Cattle infection was found to be as high as 16 per cent in the wet season, but only one-fourth of this in the dry.

In Sierra Leone *Glossina* is numerous in the bush and the more thickly populated areas, its favourite hosts being the bush-pig and, in the creeks, crocodiles. Human infection is rarely seen. In 1928 two cases occurred in the village of Aberdeen, in the Cape Peninsula, and in consequence a survey of the inhabitants of the village and its vicinity was undertaken, out of 169 from five years of age upwards examined none was found positive by blood examination, although a considerable proportion of the children showed cervical gland enlargement and of these some presented other symptoms suggestive of trypanosomiasis, nevertheless proof could not be obtained because many refused gland puncture.

In French Equatorial Africa marked changes in extent and prevalence were noticed between 1908 and 1926. These were summarized by Blanchard and Laigret who noted that there had been a serious epidemic in Upper Ogowe, Gabon, 30 per cent of the people being attacked, in the Middle Congo and the Chad Colony the disease was increasing in prevalence and was spreading northwards, in the latter about 7 per cent of the million and a half inhabitants were infected and the average annual deaths numbered 25,000. L. Tanon and E. Jamot estimated that in 1924 the carriers in the Cameroons had been reduced to a tenth as a result of treating them with atoxyl. In the preceding four years about 100,000 natives had been examined and 30,000 of them found infected, the rate of infection ranging in different localities between the wide limits of 8 and 48 per cent.

Turning to East Africa we find Dr G. D. Hale Carpenter reporting in 1925 in Uganda that there was a more or less continuous belt of infection through the southern part of the Budama district and extending northwards to the Namabala branch of the Mpologoma swamp. Also in the Bwamba area adjoining the Belgian Congo were many cases, while at Moyo there were more fatal cases than in any other part of the Mdaï district. The chief cause was the habit of the natives to hunt in the bush. Later visits to the infected area of Victoria Nyanza showed that extensive encroachments had taken place owing to occupation of uncleared watering- and landing-places. Measures were taken and in 1927 an outbreak which occurred among woodcutters of Murchison Bay was stayed by clearing the shore and prohibiting wood-cutting. In the Mpologoma area there were on the one hand in Bunyuli

people anxious to use fertile land and for this purpose reclaiming the swampy parts so that the swamp-edge was likely to be soon free of fly, but in Bugweri no precautions were taken, the people were spreading regardlessly into adjacent parts and further introduction and wider extension of the disease were practically ensured thereby. In the West Nile district cases were found and every indication that others were being concealed, but in the Madi area deaths from sleeping sickness fell from 60 in 1926 to 26 in the following year.

By 1936 the problem had shifted from Lake Victoria to the River Koich in the West Nile district. The Uganda shores of the Lake were now free except at Mjanji adjoining the Kenya border, it was undecided whether infection was maintained by immigrants from Kenya or by visitors from Uganda. At all events those parts of the Lake shore infested with *G. palpalis* are potential areas, hence the present policy includes

- 1 That a settlement shall consist of not more than ten families
- 2 At first all families congregate at one point on the Lake shore and make clearance in both directions from that point, so that the forest will recede as the settlement advances
- 3 Arrangements and supervision are under the Gombolola chief
- 4 Sufficient clearing is made to afford protection from the fly being completed within two months of occupation of the settlement
- 5 The foreshore clearing is not to be less than 300 yards long and 100 yards deep
- 6 No house is to be erected less than 100 yards from high-water level nor closer than 100 yards from the forest on the flanks
- 7 No tall crops—banana, etc.—are to be planted between the houses and the forest on the flanks, or in the clearings, but cotton, beans, ground nuts, and such-like. Tall crops are allowed on one side only of the houses opposite the Lake shore and none within 100 yards of fly-infested bush
- 8 Nobody is allowed to settle until a gland examination has been made

In the West Nile movement of infected people has resulted in the spread of the disease, and during 1936 over 1800 cases were discovered in that district.

One or two points in the recent history of the disease in Tanganyika are of interest. In 1923 a severe outbreak of the *rhodesiense* form occurred near Mwanza, which was ascribed by H. L. Duke and C. F. M. Swynnerton to decrease in the game driving the fly

to attack man This, it will be seen, would be an unexpected result of the earlier recommendations of Bruce and others to eliminate the disease by extermination of the local reservoir, game Other explanations suggested were that deficient food and the prevalence of ankylostome infestation had so undermined the vitality of the population that the local *brucei* infection of animals obtained a footing in man It was also thought that the human infection might have been introduced by movement of the Belgian troops during the Great War

In many of the patients trypanosomes were unusually numerous in the peripheral circulation and Duke put forward the hypothesis that direct as well as cyclical transmission was taking place

Three years later a survey showed that approximately 15,000 square miles of country were infected and that the disease was endemic in villages widely separated Shortage of food led to more frequent and prolonged excursions into the forest for hunting and to the streams for fishing and so the disease was spread and the local endemicity would assume more the characters of an epidemic, particularly under conditions where individual resistance was lowered by partial starvation

In 1922 extensive infection was first discovered in the Maswa-Ikoma area, the infective parasite being *T rhodesiense* and the chief vector *G swynnerton* The disease was rife in the Lake shore area as long ago as 1912-13 when over 3000 cases came under observation on the German side of the Lake In the Ufipa-Tabora area the disease had probably existed for some years before it was definitely recognized in 1924, and by the following year was known to extend over an area of at least 10,000 square miles and to have been so prevalent in certain places that villages had been abandoned on that account *T rhodesiense* was the infecting trypanosome here also, but the transmitter was *G morsitans* In the Liwale area cases were reported in 1924 and a survey made in 1925 Trypanosome and vector were the same as in the Ufipa-Tabora area Some of the villages were very heavily infected and, in fact, constituted endemic centres whence the disease was spread by movements of the inhabitants

In Kenya Colony and Protectorate *G palpalis* is the vector, in 1926-7 a survey of the shore-dwellers of the Victoria Nyanza was carried out and the disease was found to be restricted to Central and Southern Kavirondo In Uyoma (Central Kavirondo) about 100 deaths were believed to occur annually from this disease, in Southern Kavirondo the most highly infected area was Kama-kala, a subdivision of the Kaniadoto, where 12.8 per cent. of

nearly a 1000 persons examined were infected This was a dangerous focus and most of the patients in South Kavirondo were thought to have acquired the infection there Generally speaking, however, sleeping sickness is not a serious menace in Kenya, nor in Nyasaland so far as human disease is concerned, in the latter animal infection is common

Less than ten years ago (in 1929) cases of sleeping sickness were reported in the Luangwa River district of Northern Rhodesia and as the Great East Road passes through this area all who recruited labourers were required to have their employees examined medically Cases were few, seventy-three villages were inspected and over 3000 individuals examined, but only five cases were found, there is little doubt, however, that the people knew of the disease and kept some patients hidden and ten or twelve deaths occurred with symptoms pointing strongly to trypanosomiasis Increased facilities for travel, opening up of the country, movements of the men and women for harvest work all constitute a risk of spreading infection

Legends of the existence of the disease in Bechuanaland in the past seem to have some foundation in fact, though it has not been present there of late years Evidence of its existence at Semati, Lefatshe, Kacundo, Matau and Katambani is to be found in that there are sites of villages in fly-infested country no longer inhabited The story is told that "many people having died in these villages a long time ago the survivors became frightened and left" Something similar occurred as late as November 1934, when only old people were left at Siambiso, two constables had died there from sleeping sickness, though they had probably contracted the infection at Shashango where thirteen bushmen had shortly before died of it, and all who were able had consequently stampeded in every direction, the bushmen to the south, others towards Kabamukan and into the Caprivi strip, leaving only the old and enfeebled The others explained their flight by the excuse that they had gone to obtain seed grain and to pay their friends a visit

In 1935 the disease was again reported and Dr W A Lamborn went to investigate The disease was designated locally as *kgotsella*, and Dr Lamborn examined every native in the southern fly area, 258 in all, but found nothing to confirm the rumour, not a single positive film was discovered, and he doubts whether any of the reported cases was really sleeping sickness The four patients pointed out to him as suffering from *kgotsella* were certainly not cases of trypanosomiasis, the term seemed to cover

all sorts of debility, as that produced by prolonged malaria, by dietetic deficiencies, by ankylostomiasis among others Dr Lamborn states in his report

The wider rumour spreads the more it becomes magnified At Maun everyone, European and native alike, was fully convinced that the population on Chief's Island had been decimated in recent years by sleeping sickness

It was generally maintained also that isolated cases were scattered far and wide and that the tsetses in that island were larger and blacker than those on the mainland Lamborn found this also to be a myth In his detailed account he expresses doubt as to the disease having ever occurred in the area concerned, apart from the 258 natives examined in the southern fly area he examined 186 in the northern fly area and again results were entirely negative Nevertheless, seeing that deaths from it had occurred at Shashanga he advises control of bushmen from wandering through the fly areas, because these are hunting grounds of choice and the men may become infected there and spread infection widely They also penetrate fly areas in search of food-stuffs such as the pith of the wild date palm, and of papyrus and various roots It would be better to induce the natives to cultivate alternatives to the usual millet or maize which may fail when rains are deficient or when locusts invade Rice could easily be grown in the swamp areas, and varieties of sweet potato in the moist land of the swamp margin, as it grows round Lake Nyasa Cassava is another possibility

Lastly, the Sudan In 1905 trypanosomiasis was found to be spreading northward from Uganda and French Equatorial Africa and a Commission was set up to consider the question and suggest measures for dealing with it During the next four years fly-belts were mapped out and inspection posts established on trade routes from adjoining countries Next, examination of natives was introduced and any suspects could be detained In 1910 a known infected area—the Lado Enclave—was taken over from Belgium by the Sudan Government, a segregation camp was constituted at Yei, the vegetation was cleared from river banks and the place made fly-free In successive years the following progressively fewer cases were discovered and segregated 208, 140, 139 and 24, after that none was seen In 1914 the adjoining district of Kajo-Kaji was found infected and the disease extended east of the Nile, by 1924 this also was free

The southern Bahr-el-Ghazal in 1907 was free of infection, ten years later considerable immigration of natives from French

Equatorial Africa took place. Soldiers had been sent from the Sudan to quell a rising there and when subsequently dispersed they spread infection. Cases began to appear in March 1918 and soon a severe outbreak occurred, in six months there had been 255 cases, more than two-thirds (190) being persons from French Equatorial Africa. The following special measures were then adopted. Frequent inspection of natives in order that cases might be detected in an early stage, as a result the return of positives naturally rose and in the ensuing year numbered 839. The people were concentrated to facilitate frequent inspection and watering-places were cleared. Any person regarded as suspicious was segregated. Following the institution of these measures the number of cases speedily diminished, in succeeding years the records given were 276, 203, 79, 33, 8.

In 1928 Major G. K. Maurice in the Medical and Health Report stated that only one case had been found at Yei and he was a man who had contracted the infection in the Congo. No indigenous case had been discovered since 1924. A small outbreak in the Tembura district remained localized, several were traced to an old blind woman who had lain hidden, suffering from the disease in an advanced stage.

The following is a summary of the distribution of sleeping sickness in Africa in 1934-5.

Nigeria Among 381,712 persons examined 43,017 cases were found, 690 of these had been treated previously and another 4613 received treatment in the dispensaries and hospitals of the Colony.

Gold Coast There has been a large increase in recent years, due in great part to the fact that the treatment is gaining in popularity and the former hostile attitude of the natives towards it is changing. In 1929-30 sleeping sickness patients constituted 6.6 per 100,000 cases treated, in 1932-3 this had risen to 33.1, in 1934 to 91.3, and in 1935 to 177.8 or 3885 cases.

Gambia In 1935 there were 32 deaths among 1116 cases and in *Sierre Leone* only 4 cases in this and the preceding year.

As regards East Africa, in *Uganda* there were 675 cases, 72 deaths, in *Kenya* 15 cases, in *Tanganyika* 1075 cases and 342 deaths. In *Northern Rhodesia* 50 cases, in *Southern Rhodesia* none.

In *French West Africa*, including Sudan, Niger, Ivory Coast, Dahomey and Guinea, 916,393 persons were examined and 50,548 cases were found, 25,518 old and 25,030 new. In *French Equatorial Africa* nearly a million and a half (1,440,676) persons were examined (41,000 by lumbar puncture) and 13,368 new cases discovered,

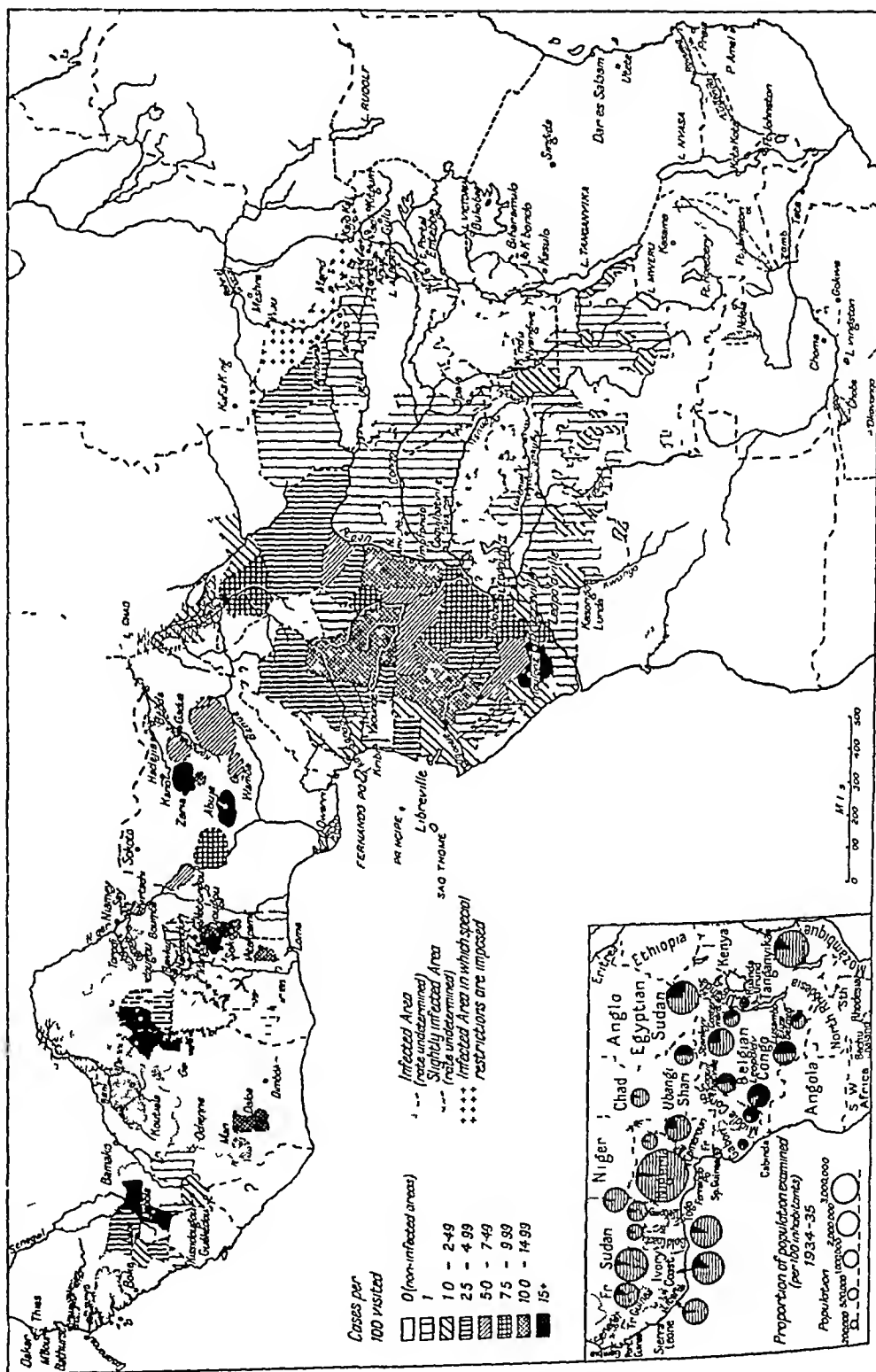


Fig 9
Map showing distribution and prevalence of human trypanosomiasis in Africa
Reproduced by kind permission from the League of Nations Epidemiological Report 1934-35

42,508 old cases were seen and treated In the *Cameroons*, under French mandate, 557,327 were examined in 1935 and among them 3614 new cases were discovered

In the *Belgian Congo* the enormous number of 4,356,270 persons were examined, 18,930 new cases were discovered and 66,775 old cases kept under observation

In *Angola* 1232 cases, 24 fatal, were seen in the coastal districts, 12 cases, one fatal, in districts adjacent to the border, and 198 cases, 14 fatal, in the interior

Dr Deutschman draws the following conclusions

In the African territories situated between the tropics, the total population of which may be estimated at 65 millions, nearly 7 millions were examined in the course of a single year One hundred and forty thousand fresh cases were discovered and treated, besides a similar number of old cases

In territories where the campaign has been going on for a long time (*Belgian Congo*, *French Equatorial Africa*, *Cameroons* under French mandate), out of nearly 15 million inhabitants, the number examined in the course of a year exceeds 6 millions

Recent surveys carried out in colonies west of the *Cameroons* show that sleeping-sickness holds a more important place among diseases in West Africa than was supposed hitherto

In certain endemic areas such as those of Kwango in the *Belgian Congo*, Nola in the *Middle Congo*, Abong M'bang in the *Cameroons*, and Djouah in *Togoland*, the results obtained from a ceaseless campaign do not yet permit us to foresee an early eradication of the disease

Agricultural prophylaxis, the importance of which is paramount, is still at a rudimentary stage In certain areas where it has been put into practice, it gives encouraging local results It meets, however, with considerable economic and administrative difficulties

7 TRANSMISSION OF INFECTION

The Vector

We have related in sufficient detail how that the natives had for years known that horses and cattle suffered from a very fatal disease the result of their being fly-struck and how Bruce had shown that this disease, nagana, was due to infection by trypanosomes inoculated by the bite of the tsetse, and how, later, seeing the trypanosomes in human subjects inflicted with sleeping sickness he was led to conclude that this too was transmitted by tsetse flies

Prior to his day, in the time of Livingstone for example, though horses and cattle were attacked, human beings probably did not suffer—the human trypanosome had not been introduced, or the animal parasite was not adapted to man (p 460) Bruce's discoveries led to a more thorough study of the life-history of tsetse

(*Glossina*) and the results of the study may be briefly summarized as follows. It was found that the female is productive for three months or more, that she does not lay eggs, but some eight or ten times during that period she drops a larva in a shaded place near water, five to ten yards from the high-water mark and away from swamps. The larva creeps into the soil, becomes a pupa and after a period varying between two and a half and ten weeks according to season and temperature, the adult emerges. The flies, if they cannot obtain blood-feeds, perish, so they tend to congregate near native huts, at fords where animals and natives gather, and they will follow native porters and herdsmen, hence they may be found in boats on lakes and rivers, or in a railway carriage where they bite the legs of passengers. [Sir Patrick Manson used to think that women were more susceptible than men because of their clothing and in 1910 he suggested that they should wear 'bloomers' to fasten round their boots and for their arms loose sleeves fastening at the wrists.] The bite is a sharp prick but the subsequent irritation is not great and the natives seem to feel it less than they do a mosquito bite. In 1908 Zupitza studied the habits of the tsetse more thoroughly in Duala, Cameroons, and found that they were most numerous in forests, in creeks, and near streams where some sun penetrated, though they preferred shade and would take shelter when a wind arose, they would fly into the open to bite, not during rain or mist or in the early morning hours, but as the sun got higher and they were worst in the late afternoon, they would enter houses and bite and fed not only on man, but on domestic animals, small mammals, monkeys, crocodiles and lizards.

Knowledge that the fly practically disappeared as the temperature dropped led travellers in Africa to traverse the fly-belts during the cooler hours of the night, when they could do so with impunity. It was observed that at nightfall the tsetse seemed to retire into the shrubs and undergrowth, but if the weather was warm they might sit up late and on that account travellers of experience would refrain from entering a fly-belt, especially on a summer night, until there had been a definite fall in the temperature.

There are several species of *Glossina*. E. E. Austen in the early years of this century described eight, namely, *palpalis*, *pallidicera*, *morsitans*, *tachinoides*, *fusca*, *pallidipes*, *longipalpis* and *longipennis*. Whether, if infection is introduced into a district previously healthy, the local tsetse would be able to transmit the disease under natural conditions is not yet determined, there is a certain amount of evidence pointing to its probability. Thus,

in Nigeria four main species are met with *G tachnoides*, *G morsitans*, *G palpalis* and *G longipalpis*, the two first in the drier north, the two latter in the wetter southern parts, and all four in the intermediate zone. The first-named has been found infected in nature and experimentally it transmitted *T brucei*, *T gambiense*, *T vivax* and *T congolense*, it is mainly responsible for epidemic sleeping sickness in the Northern Provinces. *G morsitans* is found heavily infected with trypanosomes pathogenic for cattle, and in consequence these areas, though among the most fertile in Northern Nigeria, are practically uninhabitable by stock. To bring the subject up to date, mention should be made of a very thorough study on the ecology of *G morsitans* made by T. A. M. Nash at Kikori in Tanganyika between 1927 and 1932 and in the next three to four years on others at Gadau in Northern Nigeria, comparing East and West African races of *Glossina* and dealing with seasonal, food and vegetation factors. He considers each of them in much detail, but as they are of entomological rather than of historical interest we need not do more than draw the attention of those interested in this side of the question.

The mode of transmission was for several years believed to be mechanical, that is direct conveyance of infection by the biting fly. This originated from Bruce's deduction regarding nagana, in 1895 when he discovered that this disease was due to a trypanosome he found that a healthy animal could be infected by *G morsitans* or by inoculation of small quantities of blood of an infected animal. Bruce found that "to convey the disease the contaminated flies must bite a healthy susceptible animal soon after they have been on a diseased animal." He found live trypanosomes in a fly's proboscis 46 hours after feeding, in the stomach after 118, but not after 140 hours. He concluded "The *Glossina* seems to act as a simple carrier, there is no reason for supposing that the fly acts as an intermediary host for the parasite." So much for the animal side of the question.

Ten years later when summarizing knowledge of human trypanosomiasis Bruce stated among his eleven propositions (see p. 473) that there was no proof of any developmental stage in the tsetse but that transference was mechanical, because the fly was infective for forty-eight hours only, whereas, if development in the fly was necessary, the insect would not become infective for some time after sucking the blood, also that all stages of *T gambiense* take place in man, and therefore no second host is necessary for completing the life-cycle, as in malaria.

In the Proceedings of the Royal Society (Ser B, Vol 78), 1907, we find that Minchin, Gray and Tulloch, members of the English Commission on sleeping sickness, working in Uganda, came to the same conclusion that the mode of transmission of *T gambiense* from the sick to the healthy was purely mechanical and that there was no developmental cycle in the fly. Many others had before them maintained that the tsetse was merely a mechanical carrier and transmitter of disease to animals. There is no need to give more than their names. Méguin (1875), Veth, Van der Wulp and Van Hasselt (1883), Schoch (1884), Raillet (1886), Laboulbène (1888), Blanchard (1890).

In 1910, however, Bruce having given more attention to the question began to have doubts and wrote in the *British Medical Journal* that mechanical transmission was possible, if applied at once after feeding, but that normally it was cyclical after an interval of nearly five weeks. Kleme had come to a similar conclusion, that the flies were infective for a short time after biting, then for a time were no longer so, but became infective again after an interval. Analogously, Baldrey working on the rat trypanosome, *T lewisi*, found that the rat louse became infective only after an interval of eight days. The following year the idea of mechanical transmission had been replaced by the cyclical.

Quite recently, in 1937, Darré, Mollaret, Tanguy and Mercier have recorded a case of congenital transmission which came under their observation in 1934-5. The child's parents had lived in the Chad district for thirty-two months, in October 1933 the mother became pregnant and returned to France and the child was born at Marseilles four months later. The head was large, in fact hydrocephalic, and two months later the infant had attacks of fever. The case was diagnosed as one of congenital syphilis and antisyphilitic treatment was given over a period of nineteen months without benefit. Lumbar puncture was performed in November 1935 and January 1936, and though the Wassermann reaction was negative further antisyphilitic treatment was given. In February a third puncture was made and the fluid examined for trypanosomes with positive findings and excellent results followed treatment with tryparsamide. The mother had suffered fever and the circinate erythema of trypanosomiasis.

Little need be said regarding the mode of spread of the disease. We have already mentioned the belief that the personnel of Stanley's relief column was largely instrumental in introducing the infection from the Congo to East Africa and, doubtless, ease

of transport, safety in travel and the freer movements of natives uncontrolled, contributed in no small degree to its spread. In the older days of intertribal strife, the natives stayed in their own villages except when out on marauding expeditions and the chances of extension of infection were limited. With settlement of the country, peace, civilization, easy and safe travel, improved communication and increasing demands for labour owing to commercial development of the country, infection could be carried readily from place to place. The Murchison Bay outbreak in 1928 is an example of a small local epidemic definitely attributable to this.

8 PREVENTION

As in the case of malaria the conclusion was hastily reached that when the parasite and its vectors had been discovered eradication would be easy, so with trypanosomiasis. The causative protozoon and its transmitters were known by the end of the last century and it was naturally concluded that, since where there are no tsetse there is no sleeping sickness, the obvious measure for prevention is to get rid of the fly or remove the natives out of the fly area. It would be hopeless in a work such as this to attempt to give accounts of the various means which have been tried to accomplish the former, nor are they of much historical interest. A few of the main points, however, call for mention from this aspect.

In many, we might say in most, places getting rid of the fly was quite impracticable, but the alternative proposal was carried out with success in certain parts of Uganda. The natives were moved from the sleeping sickness, that is the fly-infested, areas to healthy inland sites, and an epidemic which had cost the Protectorate some 20,000 lives was brought to an end. Such a procedure had, however, one great drawback—it meant leaving much fertile land derelict. The larger experiment at Principé and the results there attained will be taken up shortly.

Another line of procedure which theoretically should lead to good results would be eradication of reservoir hosts—extermination of big game was one suggestion (we refer to this later). Koch in 1907, having confirmed the common notion that *Glossina* fed upon crocodiles, made the fantastic suggestion that the flies might be attacked indirectly, depriving them of food by destruction of crocodiles' eggs.¹ Kinghorn and Todd the same year put forward a more sensible and more workable scheme comprising clearance of watering-places for an area with diameter of 300 yards or so,

thereby depriving the fly of shade for breeding , at the same time by treatment of patients (atoxyl was then in vogue) their blood would be freed from parasites and the biting fly would thus not contract infection from a human case , they advised the establishment of detention and treatment villages in places where there were no tsetses, and finally establishment of inspection posts to debar infected persons entering a new district

The question of extermination of game will be more conveniently spoken of in the section dealing with the various Commissions and Conferences which have functioned from time to time and the resolutions to which they gave rise

Just as the solution of the malaria problem at one time appeared simple and has become more and more complex, so has trypanosomiasis gained enormously in complexity in the course of years We know that the fly remains infective for many weeks (fourteen at least) after feeding and may be so for life and that there are several species capable of becoming transmitters , we know that if animal trypanosomes can become infective for man, an inexhaustible supply of infective material exists However careful a local government may be to restrict the movements of natives, to patrol its borders, to clear undergrowth and watering-places and crossings of rivers, to remove and treat patients, unless neighbouring States co-operate all may be rendered useless This will be obvious, but a single instance may be given The British side of the Luapula River, Northern Rhodesia, was cleared and the natives moved, but the Belgians opposite took no steps , fresh villages sprang up on their side, refugees escaped to them, caught the infection and reintroduced the disease

Other measures are directed to attacking the fly in its haunts on the principle perhaps of attack being the best method of defence This may be done by destroying their breeding-places, by clearing the bush, as already mentioned, by cultivating the land which must be preceded by clearance, and by the use of fly-traps Clearing is not always successful, for natives with their cattle will continue past the cleared area to find shade, and in dry seasons may have to follow the river-bed beyond the cleared area to obtain water In either case the benefit of clearing is lost We have said enough of destroying the breeding-places, for the present , the use of fly-traps calls for a few words An early form was that used by natives in the Sudan and spoken of by Balfour at the beginning of the century It consists of a gourd containing blood as bait Harris's trap of wood framework covered with cloth, with a slit below into which the flies enter and are caught in a wire cage

Such a trap may catch a hundred or more flies daily and as a female tsetse does not produce more than ten young in her life-time, for they breed slowly, such a reduction may be of no small benefit. Another trap is a moving screen carried by natives, the screen attracts the flies which are promptly netted by the boys. This has found a wider application recently. In Nyanza Province, Kenya, human trypanosomiasis is important and *G. palpalis* is an obstacle to occupation of the most fertile lands. Infection occurs mainly at fords and watering-places and extensive clearing of bush would be too costly and moreover would deprive the natives of wood which they must have for building purposes. The best way of freeing the bush from the fly, at the lowest cost, has been net-catching on what is known as the 'block method,' which is, briefly, this. The riverine bush is divided into blocks two miles long by clearings of 1000 yards in width. Paths are made each side of the river and are patrolled frequently by squads of natives with nets. The reduction was almost unbelievable. In one block, between October and December, 1933, over 5000 flies were caught, whereas from January to September inclusive in 1935 only seven were caught. In a control area in which the flies were caught, counted and then released, there had been no such reduction.

Most of the African colonies have special organizations under the Government for dealing with trypanosomiasis. The difficulty lies in the fact that in different places different ways are needed for dealing with tsetse and what is effectual in one place or with one species is found to fail in another place or with other species. Thus, clearing forest and thicket in the primary and main secondary foci of the fly, leaving the general front untouched, succeeds with the riverine species, *G. tachinoides*, because it depends on these foci practically all the year round, but would be quite useless with *palpalis*, for example.

In West Africa the effects of various methods have been tested over a period of years, such as excluding game from a forest pool by a ring fence, or postponing the customary grass burning till late in the dry season, or again by bush clearing. The results were not very encouraging. In parts the fly was so abundant that eradication was out of the question, there, as has been found beneficial in the northern and eastern parts of Nigeria, clearing of bush and formation of local settlements have given better results, while in other parts all that could be done with effect was to make limited clearings to protect stations and ferries. It was found that game destruction might be harmful because, if

short of food, they would congregate at drinking pools or might wander more widely than formerly in search of food. In spite of all that was done a survey revealed in 1928 several centres of the disease in the Northern Provinces and that in recent years the infection had been spreading and increasing to an alarming extent.

What has been known since 1928 as Swynnerton's policy for dealing with trypanosomiasis and the tsetse-fly menace is a development of the above. It comprises segregation and treatment of cases to cut off one certain supply of the parasite, abolition of the man-fly contact by removal of natives from the infected locality, establishing them in cleared country and controlling their movements by issue of permits, thirdly, clearing the bush along the lines of communication, and extending agricultural operations. The grass-firing referred to is not on the whole very good, it burns a certain type of thicket, drives the fly before it, and destroys a proportion of the pupæ, but with serried thicket or the ever-green type it is of little value. In fact, some recommend the planting of thicket as barriers against game on the one side and fly on the other.¹

Maclean has modified this by dividing infected areas into two categories. If an area is to be developed it is reclaimed, natives are settled on it, agriculture and apiculture established, the latter because the natives will penetrate infected forest to collect wild honey and wax. If the area is not intended to be developed, one of two plans is adopted. (1) It may be left to nature "till the disease dies out or becomes mildly endemic" [when, of course, it may become a focus of infection for important districts], (2) The people are left, but as many of the infected as possible are treated and visits of inspection are made periodically [without a large staff this is hardly practicable]. He also divides areas into 'dangerous' where quarantine is strict with or without free movement within the area, and 'infected but not dangerous' with partial quarantine and unrestricted movement.

Trypanosomiasis in Tanganyika Territory covers an area of approximately 15,000 square miles. Small epidemics occur when

¹ In Shinyanga, Tanganyika, the following has of late been adopted with success. Areas in which fires were absolutely prohibited and from which the people had been removed were set apart, round the margin of these areas a protective strip of land free of vegetation was maintained to prevent fire from spreading into the areas. If the grass in the area was allowed to grow for a period of from five to six years and was not burned during that time, tsetse fly would disappear and the land could then be occupied and cultivated. The method is applicable only to *G. morsitans* and *swynnerton* areas, but at present large districts of Tanganyika are infested by these species.

bad crops cause the inhabitants to visit the forests in search of food, for hunting in the bush is a fruitful source of infection of natives. In 1926 a special branch of the Tanganyika Medical Service was inaugurated to deal with trypanosomiasis and a policy of concentrating the population in fly-free clearings was adopted. Nevertheless extensive spread of infection took place in 1927-8 and stricter measures had to be adopted, including

- 1 Control of movements of the natives by taking a census and issuing passports

- 2 Delimitation of areas entry into or departure from which were contingent on a visa from the medical authorities that the holder was free from infection

- 3 Control at the frontier, as far as possible [This was difficult to enforce, for the frontier in places was little more than an arbitrarily made line without effective natural barriers.]

- 4 Observation posts established for examination of visas

- 5 Aggregation of natives into settlements of land suitable for development

- 6 Prohibition of recruiting of labour in affected areas

- 7 Treatment of cases

Quite at the beginning of reasoned application of control methods difficulties of dealing with the insect vector to break the chain of infection were recognized. On the Gold Coast, for example, several species of *Glossina* were found to exist and the intensity of prevalence was observed to depend to some extent on the rise and fall of the Volta, and consequently it varied with the season and, moreover, the tsetse seemed to be concentrated in certain areas—there were at least three well-marked fly-belts: a dense forest with swamp 18-30 miles from Sumbi, where *G longipalpis* was the chief tsetse, though *G fusca* and *G palpalis* were also present; secondly, the slopes of Kpeve Pass where vegetation was dense and *G palpalis* and *G longipalpis* abounded; thirdly, the savanna with localized dense bush on the Ho-Kpeve road where the same two flies prevail.

The bulk of the meat supply for the Gold Coast is imported from the Haute Volta, some 40,000 head of cattle annually, and mainly along the eastern route. Thirty days are spent in French territory in passing from the breeding areas to the Northern Territories border, nine in quarantine at the border, and three weeks *en route* from there to Kumasi and the Ashanti markets. The cattle are of the zebu type, very susceptible to trypanosomiasis. It was important to know whether infection occurred before or after the cattle entered the Gold Coast. If the former,

no measures taken in the Colony would be of much use. By examining the blood of cattle at Yeji, half way along the route, initial infection was found to be low, at Kumasi there was an increase to as high as 60 per cent. They had passed through fly-belts, the fringing vegetation of rivers and streams, and tsetse were to be found at nearly every stream crossing the 340 mile route, though large stretches of intermediate country are free, that is, infected areas, though numerous, were localized.

Nyasaland affords a good example of difficulties met with where methods which had been found successful elsewhere failed. Thus, south of Montives is an area of tall chipeta grass which is haunted by elephants and by tsetse for which it forms an adequate cover. Grass-firing which had proved very useful in Tanganyika failed in Nyasaland because, in place of dense thin-stemmed grass with relatively large amount of head, favouring combustibility, it is coarse, hard, siliceous, thin and patchy and the soil sandy. Clearing on a large scale is too costly and, owing to heavy losses in the past, the natives do not regard stock very highly. The Nyasaland scheme consists of intensive settlements at the outskirts of the tsetse area and rapid deforestation to a depth of about 1000 yards in the direction of the fly-infested country. Fortunately, human trypanosomiasis is uncommon in Nyasaland.

The beneficial effect of clearing is evidenced by what occurred at Lake Victoria and in Kasinga (Uganda) as instances. At the former reclamation was begun in 1919 and after the landing places had been cleared of bush the *G. palpalis* areas were in 1922 reopened for occupation by about 9000 natives, the majority being licensed fishermen. By 1924 there were 10,000 living there, but no case of trypanosomiasis was detected. In the latter, Kasinga, a survey made in 1920 revealed 18 per cent infection, clearings were then made and in 1922, though the population had increased by 58 per cent, no more cases of the disease were found.

The handling of the sleeping sickness problem in the Sudan has been interesting and instructive, we cannot enter into the details of it here. Suffice it that owing to its efficiency what promised to be a most serious menace was effectually checked in the Lado Enclave (now Western Mongalla). In 1924 areas still existed in Bahr-el-Ghazal and on or near the White Nile which caused a certain anxiety. It is indeed fortunate for the native population that an administration so efficient controls the situation, otherwise cases would have been many, for the *Glossina* exists in large numbers along many of the water-courses and caravan routes.

It seems a truism, but the point is often forgotten, that to a large extent the success of measures depends on the goodwill and co-operation of the natives themselves. Thus, in the Victoria Nyanza area no little harm has resulted from natives crossing over from the Kenya side into Uganda waters, unlicensed and unexamined, and establishing camps in fly-infested bush where Uganda natives were forbidden to go. The contrast between assistance and resistance on the part of natives is well exemplified at Mpologoma. In Bunyuli they were anxious to help, needing fertile land, they reclaimed swampy land and made it practically fly-free, the Bugweri, however, took no precautions but wandered into adjacent districts, reintroducing and spreading infection.

It will be interesting to describe in more detail the history of trypanosomiasis in the Island of Príncipe and of the manner in which it was combated and the results achieved. We shall see how in spite of well-meaning efforts on the part of some, they had, in the words of Rudyard Kipling, for a time at least to

Watch sloth and human folly
Bring all their plans to naught

Príncipe is an island belonging to the Portuguese, in the Gulf of Guinea. The nearest point on the African coast is San Juan in Spanish Guinea, 200 kilometres distant, and farther to the south, 240 kilometres away, Cape Lopez. It is one of a group of four islands, the other three being Fernando Pó, San Thomé and Annobon. From Príncipe to San Thomé is 130 kilometres and to Fernando Pó 200 kilometres. It is a small island, its greatest length north to south being 17 kilometres and greatest breadth 10 kilometres, and the total area only 126 square kilometres.

No case of sleeping sickness was recorded there till the nineteenth century—one record gives the year as 1820. There were no *Glossina* there before the importation of the *Mosca do Gabão* with cattle and labourers from the Gaboon in 1825. The island was owned by Dona Maria Correa who traded, chiefly in cattle, from various parts of the coast—Angola, the Mina coast and the Gaboon, especially the last which was the nearest, the animals being brought over in small, flat-bottomed boats.

For nearly half a century we hear nothing of this small island. Then in 1871 Dr Ferreira Ribeiro reported to the medical societies in Lisbon the existence of negro lethargy (*somnolência*) in San Thomé and Príncipe, both islands colonized largely from the Gaboon and the Congo and for many years the *entrepôt* of slaves for Brazil. The tsetse fly is not easily transported by ship and it

is probable that it was not present in the island in any number for some time after *cases* of the disease had entered there, that is, some fifty years previously. In the first quarter of the century and even later the vessels might be used indifferently for transporting slaves or cattle. The chief industry was cocoa cultivation and there was need of imported labour and in 1877 fresh labour was brought from Cazengo and the banks of the Quanza, and the disease spread alarmingly, and by 1885 the mortality among *serviçães* (African contracted native labourers) in the northern part of the island was very high and from 1890 onwards the disease became a veritable scourge and was likely to bring agriculture in the colony to an end. At this time the bite of the tsetse was regarded as harmless to man (see pp 79, 460, 485). In 1893-4 a further supply of 600 *serviçães* was imported from Angola, and chiefly from Cazengo where the disease was rife, and it soon began to spread. At the end of five years all had died, and nearly all from this disease. Some, of course, had been infected before coming across, others contracted the infection locally. According to an eye-witness, "These labourers were at one time dying at the rate of ten a day." In 1901 the mortality from sleeping sickness was thirty-five per mille, one-fifth of the total mortality.

By 1907 conditions were so bad—hundreds were dying each year—that the Portuguese Government appointed a medical commission under Mendes which, after a year spent in investigation, propounded measures of prophylaxis. These were not observed and the evil continued unabated to the end of 1910. In February 1911, the Governor of San Thomé, Sr Miranda Guedes, made the recommendations enforceable and travelled about the islands trying personally to convince the people of the dangers of *laissez faire*. He instituted an official brigade to assist and his measures obtained confirmation by the Central Government at Lisbon in April 1911. It was yet another instance of the futility of trying to convince a man against his will, those chiefly concerned—the planters themselves—were not convinced and on the departure of Governor Guedes the work fell into abeyance.

In August 1912, the new Governor, Marianno Martius, appointed another medical commission. As a result of their deliberations the island was divided into three zones. The blood of animals and of human beings was examined and any found to be harbouring trypanosomes were segregated. The findings may be summarized. In the first year there were 8 estates of 2106 persons examined, trypanosomes were found in 59 or 28 per cent, and incidentally filarial embryos, chiefly *perstans* (reference may be made here again

to the earlier ideas of Manson and others, p 470 *et seq*) in 326 or 15.5 per cent, and malaria parasites in 160 (7.6 per cent). Among 93 domestic animals examined 26 (27.9 per cent) showed trypanosomes. In another zone with 9 estates trypanosomes were found in 49 out of 1063 persons (4.6 per cent). Altogether in the three zones 125 cases of human trypanosomiasis were found, or 3.1 per cent of the total examined in the ten months during which the commission carried on their investigations. All these were new cases. The total attacked, old and new together, was 361 or 7.3 per cent of the island population—a marked drop from the recorded 23.5 per cent of four years before.

When considering the prevalence in 1912 we must bear in mind that in the southern zone, with five estates, was one where the only persons infected had contracted it outside, there were no indigenous cases and no *Glossina* present. Had the measures advocated by Mendes in 1908 been carried out, the disease might almost have been eradicated, so marked had been the success of Guedes's efforts. Thus, in the northern section, the worst, the incidence in 1908 was 45.8 per cent, in 1913 only 17.1, in the north-east the corresponding figures were 25.8 and 7.3, and in the east and west 20.0 and 10.3 per cent.

The commission held the opinion that the cattle were serving as reservoir hosts, 19 per cent of these were infected and within six months after they had been segregated fresh cases became rare. The loss to the planters from segregation of their cattle was so great that the decision was made to treat those infected with atoxyl with a view to rendering them non-infective. The drug seemed to act as a tonic, the experimental animals thrived well, but they did not get rid of their trypanosomes, in fact these increased in number. Some were unable to tolerate the larger doses and became blind and paretic—the last state was worse than the first.

Of the total population of 4938 there died during the ten months 286, of whom 105 were old sleeping-sickness patients.

In contrast with their previous attitude the planters heartily co-operated and this undoubtedly played no small part in bringing about the improvement. Swamps were drained, timber felled, and shelter for *G. palpalis* was thus abolished, secondary growth of scrub was cleared, *serviçais* went about in black clothes smeared with birdlime and caught many of the flies (see Fig 10), and infected domestic animals were slaughtered. Persons stung by tsetse were immediately injected with atoxyl and human patients were segregated until trypanosomes were no longer seen in their blood.

Some of the planters on whose estates were swamps even sacrificed their plantations to effect the drainage required. In the Banzu swamp tsetse were formerly very abundant and the men at work were badly bitten, ten months later, when drainage and reclamation had been carried out, it was difficult to find even a single fly and the same was observed on another estate with the Lapa swamp which before was so infested by swarms of *Glossina* that people dare not cross it.

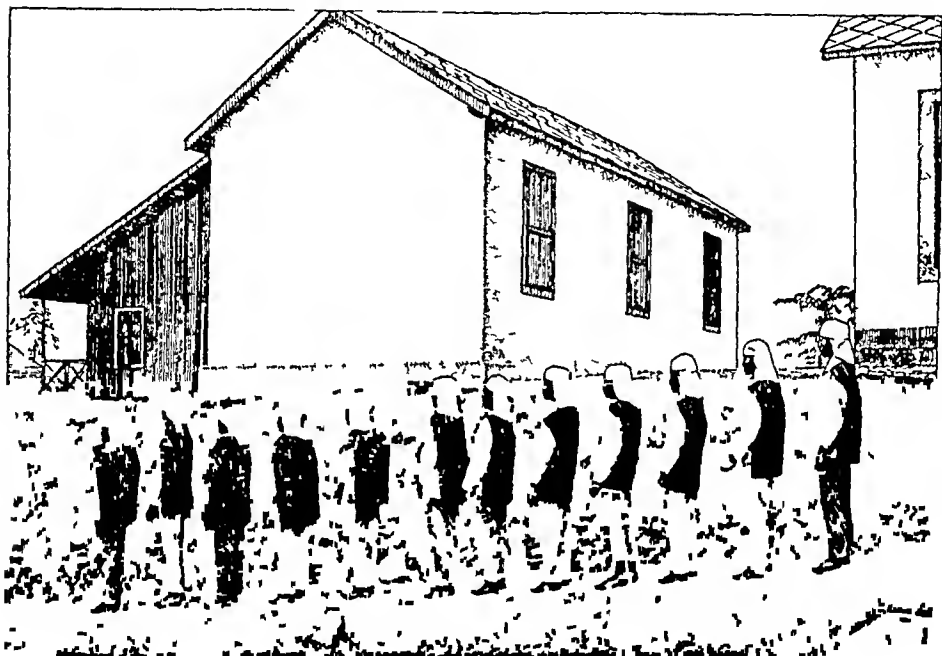


Fig 10

Members of the Fly catching Brigade in official uniform

From Sleeping Sickness in Principe, 1912-14

The following sums up the steps taken and the need therefor. In February 1911 an official brigade was created by the Governor. As the available voluntary labour was not sufficient, forty prisoners were co-opted. Though not a large force good work was done in felling forest trees and cleaning scrub and jungle. Later the force was increased to 150 by more prisoners. In August 1912 a further increase was made to 300. Natives owning plantations were indolent and indifferent and became even more so when told that the brigade would do the work if they themselves had not enough labourers to spare. Even then the property continued to be neglected, except for small patches of manioc and millet.

The human beings and the animals lived in close contact, sleeping-sickness patients would submit neither to treatment nor to segregation, saying that the symptoms were due to fetich. As many as thirty tsetse might be seen feeding on a single pig. After the plantation had been cleaned up *Glossina* would disappear and would not return unless the bush was again allowed to grow. European properties were situated close to these neglected native plantations.

Better than all generalization will be a brief account of one of the towns of Principé, Sant' Antonio. Here was no code of sanitary conventions, inhabitants were neglectful and there was no police force to compel obedience to sanitary measures. In 1905 there was an insanitary dwelling which was used as an infirmary for male sleeping-sickness patients, for females there was no accommodation. The place was condemned, but in 1912, seven years later, it was still in use and had been renamed The Hospital. Here too were detained the cattle imported from Southern Angola until their blood had been examined for trypanosomes. After strong representations two wards were rebuilt and fly-proofed (the cost was only 600 dollars) and this was intended merely as a stop-gap until the so-called Sleeping Sickness Hospital, then projected, was available. In 1911 a report stated that "the hospital of the town is under construction," and later that the Sleeping Sickness Hospital needed a mortuary, but inspection revealed that the doctor's house was still unfinished, that there was no accommodation for the staff, that there was no water laid on and no sewers. It is a little difficult to grasp what of the hospital really did exist. By August 1912 the work had been entirely abandoned and the Delegation of Health (falsely so called) was taken over by the Commission. Incidentally, there is evidence that the residence of the Delegate of Health was not of the best. "He is seriously inconvenienced in the rainy season because his rooms are flooded," says a report. The Commission started on an inspection of public establishments, gardens, streets, houses and foodstuffs. Much food had to be destroyed on account of adulteration or putrefaction, it was being sold to the public without any compunction or regard for health. Close to the walls of dwellings were masses of filth and sweepings of all kinds, mosquitoes swarmed, rare indeed was a screened house, and the inhabitants were completely indifferent, as in England three or four centuries before, domestic dejecta were thrown from the windows into the roadway. There were municipal commissioners nominally in charge of street con-

servancy, purification of sewers and drains, drinking-water supply and so forth, but nothing was attended to because the councils were composed largely of landlords whose interests clashed with the canons of hygiene. It is true the exchequer was low, but it is noteworthy that the only improvement between 1905 and 1912 was the erection of a costly Town Hall, far too fine for a town whose streets were fringed with weeds, sweepings of filth, streets unpaved and houses in all stages of disrepair. There was no slaughter-house, no butcher's shop, no public sanitary conveniences and no sewerage system in the town. Most of the municipal revenue was swallowed up by its own officialdom, there was no auditor. It was obviously necessary for the Government to step in and not only to give a grant-in-aid but to see that it was properly applied.

The plan of campaign in Principé as laid down in February 1911, will be seen from the following list of rules and regulations

1 It is compulsory to clear secondary jungle (capocrão) and fell forests [that is, to abolish breeding places of *Glossina* by removal of bush and shade], to embank rivulets and train the streams

2 Pig-breeding is forbidden and pigs are to be exterminated [to eradicate the reservoir host]

3 Dwellings are to be netted and proofed [to protect inmates from *Glossina*]. This applied to dwellings for man and beast (stables, etc.) and this had to be complied with in a fortnight

4 Labourers were to wear light-coloured clothing, covering the limbs to the wrists and ankles

5 Clearing of the land had to be carried out for at least a radius of 100 metres from the houses

6 Anyone bitten by a tsetse had to report and was given an injection of atoxyl within 24 hours [later this was reduced to a maximum of seven hours]

7 Black cloths were provided with a sticky surface for men and animals, to catch the *Glossina*. [This was known as the Maldonado process]

8 All serviços [contracted African labourers] imported or departing had to be examined for trypanosomes. [Immigration was suspended for forty days]

9 Isolation hospitals were to be established for those infected and the patients had to remain in them till free of trypanosomes

10 Examination of the blood of all inhabitants and all animals was to be carried out quarterly. In doubtful cases the gland juice also, if possible

All this appears excellent on paper but could not be carried out for the following reasons. The poorer planters could not afford to comply with the demands, there was not enough spare

labour for reclaiming waste land, felling trees, bushing, etc , planters owning pigs, instead of destroying them; set them at liberty and in consequence wild pigs, already numerous, spread over a much wider range of country and multiplied , much land was not under cultivation and had no owner , also there was much passive resistance There was not enough netting available for houses and stables , there was not enough cloth for Glossina catching, it had to be replaced each day and it proved no small hindrance to working So long as poverty was accepted as a valid excuse for non-compliance, those on the borderline, especially native planters, would dismiss some of their serviçães and *in forma pauperis* get the work done for them , lastly, the quarterly examination of the blood of the people and cattle was quite out of the question, since at the time there were only two doctors and two microscopes Later, as has been mentioned, the personnel was considerably increased

Ordinarily the bush on estates was cleared or the growth under the cocoa trees cleaned up twice a year and the trees pruned, and any stream dammed by falling trees was cleared Native planters, however, often planted without method and paid no attention to clearing, so that heavy rains soon led to a reversion to primitive conditions The brigade set about draining swamps, training rivers, canalizing streams, all of which much enhanced the productivity of the soil and the value of the plantations Clearing was no easy undertaking , paths had to be made through virgin forest to give access to labourers, and this entailed the clearing away of undergrowth, hacking through the lanas or bush-ropes which made the forests wellnigh impenetrable and when, by dint of heavy toil, passages had been made, trees felled had to be so placed and cut up that the branches would not lead to growth of secondary jungle

Not only were the pigs a favourable haunt of Glossina , they often fed on dogs and civet cats and these too were ordered for destruction and even monkeys though there was no evidence that they constituted reservoir hosts

The sticky coats proved very effectual , at first, with two men wearing them, as many as 1500-2000 might be caught, and 500 on a single cloth in a day was common The reduction was so rapid that after a week or so the number might be only a score Nevertheless its value was held to lie in the protection afforded to workers in the more dangerous places rather than in reducing the numbers of tsetse, though such large numbers being caught,

and taking into account the slow production of pupæ (see p 494), the resulting diminution must, surely, play a considerable part

Special regulations applied to domestic animals but being found impracticable they had to be modified, then changed and, finally, abandoned. The wire-netting of stables and stalls has been spoken of, further, the maximum length of halting in the streets of the town was thirty minutes, to prevent their being bitten the cattle had sticky cloths hung over back and chests [these were soon abandoned as awkward and impracticable] and if bitten they were given injections of atoxyl. This also was found impossible to carry out and finally gave way to slaughter of those found infected.

It is obvious that such stringent procedure as that detailed could only be applied with success, nay would only be applicable at all, to a small place such as Principé.

A few actual figures will suffice to demonstrate how eminently successful were the measures adopted. The following table gives the general mortality and the mortality from sleeping sickness per thousand population. The reduction in the two years following the institution of combative measures is, of course, less striking because some of the deaths in those years would be of patients infected prior to the remedial measures being applied. The figures throughout serve to show how large a part trypanosomiasis played in the mortality of the island, and we must not forget that, in addition to these, many of the infected were repatriated and died on the mainland.

Year	General Mortality	Mortality from Sleeping Sickness
1902	221	61
1903	207	84
1904	163	65
1905	173	72
1906	196	83
1907	149	54
1908	136	39
1909	164	38
1910	131	44
1911	123	65
1912	89	38
1913	69	27
Average per annum	155	56

Deaths from the disease and the prolonged treatment of patients caused very great loss to the planters, together with the general financial depression it spelt ruin for many, for the endemic meant incessant loss of life, economic risk to colonists, European and African, difficulty in procuring labour and lowered output on the plantations

The improvement is further seen on comparing numbers of carriers as determined by microscopic examination of the blood, thus in 1907 trypanosomes were found in 26.0 per cent, in 1911 in 18.5, in 1913 in 7.7, and in 1914 in 0.64 per cent only

These figures included examination of labourers, the indigenous population had fallen from about 3000 in 1885 to 800 by 1900—a drop of 73.4 per cent—and to 350 by 1907—a drop of 88.4 per cent

The results obtained in the different zones will be seen from the following table of the percentages of persons found infected

Zone	1909	1911	1913	1914
Northern	45.8	36.8	17.1	1.0
North eastern	25.8	16.2	7.3	0.3
Eastern	12.7	5.7	1.5	0.2
West Central	20.0	23.2	10.3	0.8
Town	—	4.8	2.3	0.4

9 COMMISSIONS AND CONFERENCES ON SLEEPING SICKNESS

Since the beginning of this century several Commissions have been set up and Conferences held to investigate, consider and report upon trypanosomiasis and, in particular, human trypanosomiasis. As records of stages in the advancement of our knowledge of this disease they are of importance historically.

Necessarily, much of what these Commissions and Conferences accomplished has been presented already in the foregoing pages, but it will not be amiss to give a brief résumé here, bringing the main facts together within a small compass.

In April 1902 a deputation from the Royal Society waited upon Lord Lansdowne to ascertain whether His Majesty's Foreign Office was prepared to consider favourably a recommendation emanating from the President and Council to investigate sleeping sickness in Uganda. The Secretary of State expressed his approval of the scheme and a Commission was appointed consisting of Dr G. Carmichael Low, Dr C. Christy and Dr (now Sir) Aldo

Castellani These appointments were made on the recommendation of the Malaria Committee and, in fact, the Commission worked under the direction of the Malaria Committee of the Royal Society. This was the Royal Society's First Sleeping Sickness Commission to Uganda, 1902-03.

What may be called the Royal Society's Second Commission worked also in Uganda, from 1903-06. The first members were Lieut-Colonel David Bruce, R A M C and Dr Nabarro. They arrived at Entebbe on 16th March, 1903, to continue the investigations of Low, Christy and Castellani. In May the same year they were joined by Captain Greig of the Indian Medical Service and on the 28th August Colonel Bruce left for England, followed by Nabarro in November. A year later, 15th November, 1904, Captain Greig also returned, leaving Lieutenants Gray and Tulloch to carry on. A C H Gray had joined the staff in March 1904, and Lieutenant Tulloch joined in the succeeding January. In March of the following year Tulloch became infected and on 3rd April had to come home to England, Gray accompanying him. Professor Minchin had joined the Commission on 3rd April, 1905, to work on the relationship of tsetse fly to *T. gambiense*, he was engaged on this for eight months and left on the 6th December. The Second Commission may thus be said to have faded away.

At the suggestion of Lord Ripon, then Secretary of State for the Colonies, a Third Royal Society's Commission was formed in 1908, consisting of Colonel Sir David Bruce, Captain A E Hamerton of the Royal Army Medical Corps, H R Bateman and F P Mackie of the Indian Medical Service, and Lady Bruce, with Staff-Sergeant A Gibbons and Mr James Wilson. They were to continue the investigations, utilizing the laboratory which had been built for the previous Commission in 1906. The members left England in September and in a little over a year, in November 1909, Mackie returned, followed in December by Sir David and Lady Bruce. Captain A D Fraser, Drs Hale Carpenter and Lyndhurst Duke joined the staff and carried on the work when Hamerton and Bateman left in August 1910. In 1911 Miss Muriel Robertson went out to study the development and transmission of pathogenic trypanosomes.

Next in chronological sequence mention must be made of the German East African Sleeping Sickness Commission which in point of time actually comes between the second and third Commissions of the Royal Society, as its operations were carried out in 1906-07. The report of its members, published in 1909, was a

volume of over 300 pages, with numerous illustrations mostly from photographs, taken by Professor F. Kleine, of the scenery and patients. Professor Robert Koch wrote on ætiology and, aided by Professor Kleine, on measures of prevention, Professor M. Beck on symptoms, diagnosis and treatment by atoxyl.

To save returning later to the question of German Commissions we may here again anticipate, by departing from the strictly chronological order, and refer to the Togoland Sleeping Sickness Commission of 1908-10, with Dr. Zupitza at the head. Reports written or edited by him were presented quarterly, recording progress, the numbers of patients seen, the results of treatment, the measures adopted, and so forth. In August 1911 the following agreement was drawn up between the British and German Governments to combat the disease in West Africa—the Gold Coast Colony, the Ashanti Protectorate, the Northern Territories of the Gold Coast and Togoland. The terms were these:

The said Governments shall—

1. As far as the means at their disposal allow, cause the most thorough investigation to be made by expert medical officers into the extent of Sleeping Sickness in the Colony and Protectorate aforesaid,

2. Keep each other informed of the incidence, extent and possible spread of Sleeping Sickness in these dependencies,

3. Treat patients suffering from Sleeping sickness and take preventive measures against the disease according to the means at the disposal of the local Governments concerned,

4. Give instructions to their respective local authorities, that natives of one dependency found to be suffering from Sleeping Sickness in the other shall be treated free of cost in accordance with the arrangements made under paragraph 3.

5. The two Governments shall have the right to turn back at the frontiers of the above-mentioned dependencies native subjects of the other Power proved or suspected to be suffering from the disease,

6. The two Governments shall have the right to impose such restrictions on the frontier traffic as may be deemed necessary to prevent the spread of Sleeping Sickness, but they undertake to communicate to one another without delay the terms of any restrictions so imposed.

At the same time as the Germans were investigating sleeping sickness in East Africa, a French Mission had been working in the French Congo between 1906 and 1908. Their report, written jointly by Gustave Martin, Lebœuf and E. Roubaud, was published by the *Société de Géographie* in 1909 in a volume of over 700 pages. It dealt with the investigations in eleven sections concerned, in order, with the Organization and Programme of the Commission, the Geographical Distribution of Sleeping Sickness and of biting flies in the Congo, Epidemiology and the Method

of Spread, the Microscopical Diagnosis of the disease in Man (by examination of blood, gland juice and cerebrospinal fluid), a separate section was given up to discussing the value of gland enlargement in human sleeping sickness, followed by one on the Clinical Aspects of the disease and on Treatment, on the Biology of *Glossina palpalis* and its pathogenic trypanosomes, and on Prophylaxis

Passing mention only need be given to a Spanish Commission under Gustav Pittaluga which visited Spanish territory in the Gulf of Guinea from June to October 1909, where they found many cases in Fernando Pó and on the mainland on the Muni River. In the former horses also were found to be harbouring trypanosomes. Accompanied by Drs Illéra and Raman, Pittaluga went first to Santa Isabel in Fernando Pó and stayed there for a fortnight, then to Elobey, an island at the mouth of the Muni River, and thence up the river as far as Bata and the River Campo which then formed the southern boundary of the German Cameroons. Finally, they again visited Fernando Pó and in October returned to Spain. Only 373 persons in all were examined. The report, issued in 1909, is entitled *Informe de la Comisión del Instituto Nacional de Higiene de Alfonso XIII enviada a las posesiones españolas del Golfo de Guinea*.

Reference has already been made to the Portuguese Commission under the Directorship of Dr Corrêa Mendes to Príncipe and the work done there between 1908 and 1911.

The Belgian Scientific Mission to Katanga (1910-12), under J Rodham, C Pons, F van den Branden and J Bequart, performed some pioneer work. They showed that in Lower Katanga the existence and spread of sleeping sickness seemed to be strictly bound up with the presence of *G palpalis*. On the plateau of Biano *G palpalis* does not extend beyond 1140 metres, while *G morsitans* is found up to 1600 metres. Cases of the disease found in villages 1200 metres up are imported cases. It was concluded that the reasons for the non-infectivity of *G morsitans* on the upper Katanga were, partly, the special biological characters of the insect, and partly the climatic conditions in which it lives. The report of the Commission issued at Brussels in 1913 showed that in the laboratory *G morsitans* could be infected as readily as *G palpalis* is in nature, but it was rare for the former to have its first feed on an infected host since it lived chiefly on animals whereas the latter lived preferably on human blood and would

frequently find an infected host at its first feed. It was found further that with *T. rhodesiense*, a protozoon as virulent for man as for animals, *G. morsitans* readily infected the animals, many of which on the savannah were reservoirs. Hence in nature, *G. morsitans* did not appear to be a menace to man in the Lower Katanga, where the human disease is occasioned by *T. gambiense*. The Commission recommended, therefore, that for prophylaxis the people should be protected against the bites of (possibly) infected *G. palpalis*, that in regions at present free from the disease the flies should be prevented from becoming infected, and that this entailed prevention of introduction of the infection from Rhodesia, as *T. rhodesiense* would be rapidly disseminated by the numbers of *G. morsitans* present.

In this connection we may refer to an account of Trypanosomiasis in Southern Rhodesia, published by A. M. Fleming (*Trans. Roy. Soc. Trop. Med. and Hyg.*, 1913, p. 298) in which the author states that *G. morsitans* was the only tsetse found and that the fly areas are in the northern parts, each limited and widely separated. The reasons for these limitations were not known. Fortunately, however, these areas were sparsely populated by natives and were remote from European settlements. He concluded that human trypanosomiasis undoubtedly existed in the Sebungwe district, but the infection was small in relation to the population, the area of infection seemed to be limited to villages along the banks of the Busi River. Investigations tended to show that fly-sickness of stock had been known for many years, but that infection of man was probably of comparatively recent origin, and, finally, that if extension beyond its then boundaries was to be prevented it would be well to remove the entire population of the fly-belt.

Next in point of time comes the expedition of the Liverpool School of Tropical Medicine to the Gambia in 1911. This can hardly be called a Commission to study the disease in general, as did the others, but the work it accomplished was of great value. The members were J. L. Todd and S. B. Wolbach and the main objects were to determine the value of gland puncture in the diagnosis of human trypanosomiasis and the incidence of the disease in the Gambia. They reached Bathurst on 4th February, 1911, and began work on the 10th. They spent a little over three months in the Protectorate and examined altogether 12,298 natives in 95 towns and villages. Trypanosomes were found in 79 and in another 21 gland puncture was not allowed, but the diagnosis was taken as certain, and it may be said that between

8 and 9 per mille of the population of the Gambia were infected. They found gland puncture a very useful and reliable means of diagnosis and that in the Gambia preventive measures should include continued examination of the whole population, establishment of villages for isolation, observation and treatment of cases and an adequate staff to carry out these duties.

The Commission in Rhodesia, the Luangwa Sleeping Sickness Commission of the British South Africa Company, accomplished much of importance. The members were Dr A May, Principal Medical Officer, Northern Rhodesia, Dr A Kinghorn of the Liverpool School of Tropical Medicine, Dr J R Leech of the Rhodesia Medical Staff, a trained entomologist and bacteriologist, and Dr Warrington Yorke. Without entering too deeply into the details of their investigations we may state the conclusions arrived at. They found that infection in the Luangwa Valley was transmitted by *G. morsitans* and nearly 5 per cent of the flies became permanently infected, that no mechanical transmission by them occurred after twenty-four hours, but that they became cyclically infective between eleven and twenty-five days after feeding, the average being fourteen days, that this infectivity was retained throughout life and that the insect is infective at each meal. The development of the trypanosome in the fly was found to be markedly influenced by temperature, being favoured by high temperatures between 75° and 85° F. They found the human trypanosome in certain wild animals, notably waterbuck (*Cobus ellipsiprymnus*), hartebeest (*Bubalis caama*), impala, warthog (*Phacochærus*) and a native dog, but there appeared to be great differences in susceptibility. Kinghorn and Yorke never found the zebra infected, but J C R Buchanan, who investigated the trypanosome infection of wild game in the Ruckwa Valley, a centre of *rhodesiense* trypanosomiasis in the Ufipa district, badly infested with *G. morsitans*, found more than 50 per cent of the waterbuck infected and, in lesser degree, impala, topi, zebra, eland, bushbuck, giraffe and puku.

We see, therefore, and Roubaud (v s) has shown that the presence of numerous tsetse in a region is not *a priori* a danger to man or to domestic animals. Certain animals are better receptors than others. Though climatic factors are the same for all, different species react differently.

The final report of the Commission appeared in 1913 and was divided into six sections. The first and second by Kinghorn and Yorke dealt with the human trypanosome and those of game and domestic stock, the third with trypanosomes found in wild *G*

morsitans, *T. rhodesiense*, *T. ignotum* (*T. simæ* of Bruce, 1912) and *T. pecorum* (*T. congolense* of Broden, 1904) were transmitted by the same fly in nature. The fourth section contained a description of the trypanosomes found. In the fifth Kinghorn, Yorke and Ll Lloyd dealt with the development of *T. rhodesiense* in *G. morsitans*, and the sixth was concerned with the entomologist's report. Appendices dealt with experimental attempts to transmit by Tabanidæ and *Ornithodoros moubata*.

Finally, in 1911, the Secretary of State for the Colonies, Mr Harcourt, asked the Royal Society to take charge of work directed towards ascertaining the relation of African fauna to the maintenance and spread of human and animal trypanosomiasis. The members appointed were Sir David and Lady Bruce, Major A. E. Hamerton, Major D. Harvey, Dr J. B. Davey, with Staff-Sergeant Gibbons and Mr James Wilson. They began work in Nyasaland in January 1912 and continued till 26th March, 1914. One of the chief conclusions of this Commission was that, so far as the region which they had investigated was concerned, the wild game constituted the main, if not the only, reservoir from which the tsetse fly draws its infectivity and they recommended that efforts should be made to reduce, as far as possible, the number of wild animals in the tsetse area.

Apart from the Commissions whose constitutions and work have been described there have been three International Conferences and one Conference of Governors of British East African Territories.

The first of these is known as the Foreign Office Conference of 1907-08. This was an International Conference summoned by His Majesty's Government with the primary object of concerting a common policy and devising administrative measures to be put into force by the officers of the respective Governments in the areas infected with or menaced by sleeping sickness. The Conference met in London in June 1907 and again in March 1908. One important outcome of this was the establishment of the Sleeping Sickness Bureau which was to be a central international Bureau "to extract and circulate all new literature on sleeping sickness," but the various countries were unable to agree as to its location nor did they see the need for it. Thereupon Lord Elgin, the Secretary of State for the Colonies, established a British Bureau.

In 1911 it was suggested that what was being done for sleeping

sickness might be extended to include other tropical diseases, and as a start a quarterly Kala Azar Bulletin was issued dealing with Leishmanial diseases, Kala Azar and Oriental sore. After this, plans for further extension of the functions of the Bureau matured quickly and in 1912 the Bureau moved from rooms in the Royal Society's buildings to the Imperial Institute, South Kensington, and in July its title was changed to the "Tropical Diseases Bureau". In 1926 further extension was made to include the distribution of information on sanitation in general and tropical sanitation in particular, and the "Bureau of Hygiene and Tropical Diseases" came into being.

As the Sleeping Sickness Bureau it produced four volumes of information on this subject, since 1912 there has been issued monthly the *Tropical Diseases Bulletin*, and since 1926 also a monthly issue of the *Bulletin of Hygiene*, each making a volume of 800-1000 pages every year and from their steady increase in popularity it would appear that both fulfil a real want.

The primary function of the Bureau is to collect information regarding hygiene and tropical diseases, to collate, condense and, where necessary, translate this information and to make it available to officers of the medical and health services of the Empire and to research workers and others concerned, whether in British or foreign countries. To this end, the Bureau surveys the world literature on hygiene and tropical diseases, aiming to miss nothing of value, no matter where or in what language. In addition to the large number of abstracts—some thousands annually—articles and critical reviews are published from time to time dealing with important subjects and with the progress of knowledge in tropical and public health matters.

Since 1930 there has been issued annually a supplement abstracting and reviewing the Reports of the Medical and Health Departments of the British Colonies, Protectorates and Dependencies.

Mention may be made also, incidentally, of other work of the Bureau in replying to inquiries on tropical and health questions from all over the globe and in obtaining or lending reprints on important matters to those interested. The *Tropical Diseases Bulletin* is now in its twenty-eighth year of issue, is without a rival since no other abstracting journal has attempted to cover comprehensively the field of tropical medicine. For some years the Bureau dealt in like manner with the literature relating to diseases of animals in the tropics and from 1912 to 1930 published quarterly a *Tropical Veterinary Bulletin*, but in 1931, when an Imperial Bureau of Animal Health was established, it took over this work.

and the Bureau of Hygiene and Tropical Diseases now deals with animal diseases only so far as they are communicable to man

Two International Conferences, one in London and one in Paris, have been held under the auspices of the Health Organization of the League of Nations. The former met at the Colonial Office, London, from 19th to 22nd May, 1925. Representatives of the Colonial Administrations of Belgium, France, Great Britain, Italy, Portugal and Spain discussed the financial and administrative possibilities of despatching a special mission for the epidemiological study of sleeping sickness in Equatorial Africa. The Conference also considered proposals for liaison with, and co-operation between, the Sanitary Administrators in Africa. As a result the headquarters of the First International Sleeping Sickness Commission were established in Entebbe, Uganda, with Dr H. L. Duke, as Chairman, and Dr Lavier (France), Professor Kleine (Germany), Dr Van Hoof (Belgium), Dr Prates (Portugal) and Dr Peruzzi (Italy) as members. The aims of the Commission were: Exchange of information and critical correlation of results, such as could be carried out by a central and unbiassed body, whereas spasmodic efforts by isolated workers often prove abortive. Also specially suitable places might be selected for particular points of investigation. Thus, it was thought that clinical conditions and therapeutic measures could be well studied in the French and Belgian Congo, the behaviour of the parasite in the insect vector in Uganda, in other districts measures of control and attempts at eradication. From a consideration and discussion of the results obtained hope was entertained that analogous measures might be applied, *mutatis mutandis*, in other infected areas. Without going too minutely into detail we may say that this Commission finished its labours in 1927, they published an Interim Report in March 1927 and a Final Report in March 1928, recommending the following measures of control and prevention:

- 1 Control of movements of natives in sleeping sickness areas, each native to be supplied with an identity card as a passport
- 2 Census of infected natives to be made and kept up to date
- 3 Compulsory treatment of all cases
- 4 Removal from heavily infected zones
- 5 Limitation of bush-clearing to frequented places, especially in *palpals* regions

The Second International Sleeping Sickness Conference met in Paris in November (5th-7th) 1928. It was attended by delegates from Belgium, France, Great Britain, Italy, Portugal and Spain.

The members were *Belgium* M Halewyck de Heusch, Director-General, Ministry for the Colonies, Dr E van Campenhout and Professor Rodhian *British* The Right Honourable W Ormsby Gore, Parliamentary Under-Secretary of State for the Colonies, Dr H Andrews, Dr (later Sir) Andrew Balfour, Dr (later Sir) Arthur Bagshawe, Sir George Buchanan, Dr H L Duke, Mr C J Jeffries and Dr H H Scott *French* Dr Abbatucci, Dr Boyé, Professor Brumpt, Dr Cognacq, Dr Ledentu, Dr Martin, Professor Mesnil and Dr Roubaud *Italian* Professor (later Sir) A Castellani, Dr Lutrario, Dr Peruzzi and Dr G Zucco *Portuguese* Dr A Aires and Dr A Kopke *Spanish* Dr L R Illera

For the information of members reports were furnished on Trypanosomiasis in the Belgian Congo, on the Progress of Investigation in the British Colonies and the Condition of Sleeping Sickness in the various British Colonies and Protectorates, on Sleeping Sickness in the Sudan, on the Campaign against Sleeping Sickness in French Colonies and Mandated Territories (Togoland and the Cameroons) and on the work in Spanish Guinea and Fernando Pó

Two sub-commissions were formed, one to deal with administrative measures, the other with research. As a result a programme of research was elaborated the details of which are to be found in the report of the Conference issued by the League of Nations in December 1928. The general recommendations for control of the disease in African Dependencies contained in the Final Report of the First International Commission (see above) were discussed.

A survey of the conditions in Africa showed that in the Victoria Nyanza infected area extensive encroachment had taken place, uncleared watering- and landing-places were being used and plantations opened up. Hence the area of infection had extended. Again, salt traffic among the natives was causing concern. Clearings on the rivers were therefore increased, persons entering the Congo were examined and permits issued for the purchase of salt, and precautions taken (not always effectually) to prevent introduction of infected persons to and from the Belgian Congo.

The Conference recommended adoption of the general suggested measures of control in the following form

I Control over the movement of natives. This implies

- (i) Enumeration of natives, carried out by the administrative authorities
- (ii) Adoption of an identity book, card, etc., for each native, containing particulars as to health, which could serve as a medical passport

- (iii) Delimitation of areas, for entry into and departure from which a medical authorization will be necessary
- (iv) Close co-operation between medical and administrative authorities—without which any prophylactic measures would be ineffective
- (v) The establishment of observation posts for medical examination and medical control of natives

II Control and treatment of infected natives, both of which should be as complete as possible, for this there are required

- (i) Adequate medical personnel
- (ii) Powers to enforce the medical examination and treatment of natives
- (iii) In case of necessity, the power of withdrawal of authorization to travel

III Effective maintenance of clearings at watering-places, at river crossings and around villages

IV If considered by the local administration to be indispensable, heavily infected zones to be abandoned and the people removed to a more favourable situation in the vicinity

These suggested measures, it will be seen, are merely elaborations of the recommendations of the First International Conference

In November 1933 a Conference of East African Governors was held at Entebbe to consider various aspects of the question of Tsetse and Trypanosomiasis (Animal and Human) Research. Their report was submitted in July 1934 to a Subcommittee of the Economic Advisory Council, composed of Mr Francis Hemming, C B E, Sir Guy Marshall, C M G, F R S, Mr F G Lee, Sir Thomas Stanton, K C M G, Chief Medical Adviser to the Secretary of State for the Colonies, and Dr C M Wenyon, C M G, C B E F R S. Mr D H F Rickett was secretary to this subcommittee.

The report and the deliberations of this subcommittee upon it are of sufficient importance to call for an account of some details.

It is noted that, from causes not really understood, epidemics of great virulence have occurred in the first decade of the present century in Belgian, French and Portuguese territories in the Congo and in the Uganda Protectorate, and epizootic outbreaks among domestic stock had been still more frequent, resulting in great loss and consequent impoverishment and moral degeneration of the native communities.

The relations between the various species of parasite and also of human to animal trypanosomiasis were once more discussed. It is known that man is, for all practical interpretation, immune to infection by *T. congolense* and *T. vivax*, important trypanosomes of stock, and, *vice versa*, that *T. gambiense*, though it can infect both domestic and wild animals, is not strongly pathogenic for

them as it is for man. As regards the relation of the human parasite *T. rhodesiense* to the animal trypanosome *T. brucei*, this is important not only in its bearing on the direct question but also on the part played by game as a reservoir of infection. British workers incline to the view that they are in fact the same, foreign authorities that they are different.

Control methods are of three kinds

I *Administrative*, such as evacuation of the population from an infected area, control of the movements of the people in search of work, etc., the clearing of watering-places and concentration of settlement. It has been found that a settlement with a minimum population of 3500–4000 is large enough to secure freedom from fly roughly two years from its establishment and the general view of the Conference was that organized settlement and development was, under usual conditions, the most important general preventive measure, if combined with improvement of agriculture and animal husbandry.

II *Control of Tsetse Flies*. Enough has been said of the details on this in the foregoing pages, here the matter may be summed up in the conclusion of the subcommittee: concentration of population must be coupled with active measures for reclaiming infested areas and for holding up the advance of the fly over a wide front. Promising results are being obtained from organized grass-fires, differential (as opposed to wholesale) clearing, fly and game barriers formed by dense strips of thicket, fly traps and "densification of vegetation," that is protection from grass-fires for several seasons, the growth of bush becoming so dense that it is unfavourable to certain species of tsetse (see footnote, p. 500).

III *Control by Chemotherapy, i.e. drug treatment*. This too need not be enlarged upon.

The question of Protozoological Research was minutely considered and the conclusion was reached that the Human Trypanosomiasis Institute at Entebbe had largely fulfilled its purpose and though research might still be carried on there, the maintenance of a permanent research institute devoted solely to trypanosomiasis would be disproportionate to the medical needs of the Protectorate and that it should be closed at the end of 1935.

Meanwhile important investigations were pursued in other parts of Africa, notably those of Dr J. F. Corson at Tinde in Tanganyika, on natural immunity, spontaneous cure and immunity in man, and particularly the relationship between *T. gambiense*, *T. rhodesiense* and *T. brucei*, approaching the subject from an angle differing

somewhat from that of Dr H L, Duke, and studying the conditions, if any, under which one of them may assume the character of either of the others (morphologically they are not distinguishable) Though it would seem rather a *petitio principii*, it is held that *T rhodesiense* is only distinguishable from *T brucei* by the fact that at present *T brucei* is not known to give rise to infection in human beings, although British workers (see above) maintain that they are really the same Corson's investigation is not to determine whether they are one and the same but under what conditions one can become the other First, he maintained *T brucei* in animals for a certain period and tested its capacity of infecting man (himself and Mr H C Smith of the Veterinary Department) After being kept up in animals by inoculation for four and a half years the trypanosome was still transmissible (to animals) by the tsetse, but neither he nor his fellow volunteer became infected Next, he tried to discover whether a human strain, *T rhodesiense*, maintained by a series of inoculations of animals would acquire the characteristics of *T brucei* and lose the power of infecting man After nineteen months' passage in sheep, goats and guinea-pigs, it was still infective for man

Finally, in 1936, from the 29th to the 31st January, another Conference of the Governors of East African Territories was held at Entebbe, Uganda, to discuss the Conduction of Research on Tsetse and Trypanosomiasis in East Africa At this Conference a programme of work was drawn up and arrangements made as to the places best suited for carrying on the work

10 THE TREATMENT OF HUMAN TRYPANOSOMIASIS

Before the causative parasite was known nothing was done, or in fact could be done, in the way of scientific treatment, nor even when the vector was discovered until information had been acquired as to its habits and habitat In these early days segregation camps were established and little else When more information was available, suggestions on lines analogous to those applicable to malaria were made with a view to prevention (1) To deal with the fly which carried the trypanosome, as *Anopheles* is dealt with as the vector of malaria (2) To deal with persons who harboured the parasite, protecting them by segregation, nets, or otherwise, from becoming a source of infection through allowing *Glossina* to bite them (3) To deal with the parasite itself in the patient, rendering his blood free so that he may not become a source of infection if bitten by *Glossina*, or

briefly to destroy the cause, or render susceptible persons immune, or cure by some drug

So in the case of animal trypanosomiasis preventive measures were suggested on the lines of getting rid of the reservoir (game), getting rid of the vector, and removing cattle, horses, etc., to a safe distance from the fly-infected country

From the historical aspect there is no need to add to what we have said already on the question of the vector and the ways of dealing with it. There remains to speak of the drugs which have been tried from time to time and these have been many. We shall not attempt to give an account of their actions and uses in any detail, such hardly come within the scope of their history. A large proportion are arsenicals in some combination or other, or, of later date, antimonial compounds. The following is not a complete list but contains the most important of the drugs which have been proposed and tried

Arsenicals Liquor arsenicalis, atoxyl, soamin, tryparsamide, acetylarsen, Hoechst 2574, cyclosan, treponarsyl, stovarsol, novatoxyl, B R 68 (Binz and Rath)

Antimonials Antimosan (Heyden, 668), stibosan, stibenyl, styryl compounds, styryl quinolines

Some of these, *e.g.* Hoechst 2574, cyclosan, stibosan, stibenyl, and tryparsamide are pentavalent compounds, others are trivalent and, speaking generally, the latter have proved much the more active, so much so that most of the pentavalent have been practically given up. Yorke and Murgatroyd in 1935 adduced evidence indicating that the pentavalent arsenicals owe their therapeutic activity to their being reduced to the trivalent form, as in the case of tryparsamide. An enormous amount of experimental work has been done, mostly—at least at first—on small laboratory animals, and unfortunately it has been shown repeatedly that compounds giving excellent results on trypanosome infections of these animals may prove altogether ineffectual in larger animals, in the field, and in man.

Professor Warrington Yorke and his co-workers, Drs Murgatroyd and Adams, did good basal work in 1929 in devising a method by which trypanosomes could be kept alive a sufficient length of time for valid testing of drugs *in vitro*. They were able to show that the primary cause of the rapid death of trypanosomes in concentrated suspensions is exhaustion of the glucose content of the serum (they used the serum of rabbit, sheep, horse, ox or pig). Exhaustion of other constituents and excretion of auto-toxins by the parasites probably play a part also. Provided,

however, the initial concentration of trypanosomes is not too great, that is more than 1000 per cmm, their numbers remain practically unreduced for twenty-four hours at 37° C. Thereafter the number falls but even for three or four days enough remain to allow of infection experiments on mice. This is quite aside from the application of laboratory tests of drugs to their use in the field.

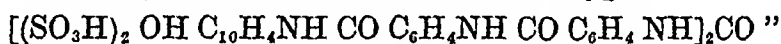
Before arsenic was introduced for treating these cases every sleeping-sickness patient was doomed. In the early days *Liquor arsenicalis* was used and A. R. Cook records the case of a patient whose "gland juice was swarming with trypanosomes", increasing doses were given till $1\frac{1}{2}$ grains of arsenious oxide were given at a single dose. Symptoms disappeared and the patient lived to such good purpose that he married and twenty years later was still alive.

In the course of time many drugs were tried for eradicating trypanosomes from animals, some were ineffectual, some, such as sodium arsenate, caused toxic symptoms and were liable to set up local sloughing. Wolferstan Thomas in 1904-05 searched for other arsenic compounds to find one which would be effectual without these drawbacks. Several commercial products were obtained from Germany and the best results followed tests with one known as *atoxyl* (a trade name), a preparation which had been used in Germany for the treatment of anæmia and skin diseases. Thomas, finding it trypanocidal in animals, suggested its use in man, in May 1905. Atoxyl is, constitutionally, sodium β -aminophenylarsonate and has the formula $\text{NH}_2\text{C}_6\text{H}_4\text{AsO}(\text{OH})\text{O Na}$. For the treatment of human cases of sleeping sickness a 20 per cent solution was used, injected subcutaneously after being warmed to blood-heat. The dosage as given by J. L. Todd was 0.6 c.c. daily till signs of intolerance began to appear. Thereupon the dose was reduced till tolerance was obtained and this was kept up for varying lengths of time according to the needs of the case.

The previous year (1904) Ehrlich and Shiga prepared a substance which they called Trypanrot, Trypan Red, with the terrifying composition Sodium 3-sulphodiphenyldiazobis- β -naphthylamine-3,6-disulphonate. This was active against trypanosomes *in vitro* but was not used in practice. Ehrlich, hearing of Wolferstan Thomas's results on *T. gambiense* infections in mice, came over to Runcorn to see the work and on his return to Germany took up the researches which led to the preparation of arsenophenylglycin and finally to salvarsan.

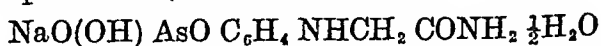
After atoxyl came *soamin*, a preparation having the same chemical composition as atoxyl and, from experiments carried out in the Sudan on rats infected with trypanosomes, it seemed to be efficacious also when taken by mouth

The next two drugs calling for mention were non-arsenicals, the first as a stepping-stone to the second. In 1912 L. Breiger and M. Krause discovered a dye, a chemical substance non-toxic to man even in large doses, known as *trypasafrol*. Experimentally, good results were obtained in rats infected with *T. brucei* and it has a parasitocidal action when taken by mouth, moreover it does not readily deteriorate. The fact that it contains no arsenic formed a new point of departure, for the trypanocidal effect showed that it was not necessary to link an organic molecule to arsenic to attain this. The other non-arsenical preparation which came to the front a decade later and has maintained its reputation in the treatment of human trypanosomiasis is that known as *Bayer 205* or *Germanin*. According to Martindale it is "a complex organic urea, probably a derivative of the type



Testing trypanocidal drugs has usually progressed in three steps, first, their action on small laboratory animals experimentally infected—a septicæmic type of disease, next, on larger animals in whom the disease is a tissue infection like that of human sleeping sickness, and, thirdly, in human patients infected in nature. Though Bayer 205 had a powerful action on both *gambiense* and *rhodesiense* and was particularly effective in the early stages, it would not cure patients in the more advanced stages, probably by reason of its low diffusibility into nerve tissue. Others, Tanon and Jamot among them, reported that though useful as a trypanocide its administration might be attended by signs of renal mischief which might not be transient, yet others, Kellersberger for example, found that the drug was badly tolerated if infection by malaria or ankylostomes was present.

Close on the heels of Bayer 205 came another drug, a pentavalent arsenical, *tryparsamide*, discovered the year before by Jacobs and Heidelberger. Tryparsamide is Sodium N-phenylglycinamide-p-arsonate, with the formula



It has the advantage over germanin of acting in later stages of the disease, but otherwise has the same drawbacks as the earlier arsenicals. The drug became very popular among practitioners in sleeping-sickness regions in Africa and high proportions of cures

were reported Ledentu of the Pasteur Institute, Brazzaville, noted, however, that in contradistinction to atoxyl, for example, an insufficient course of the drug provoked quite definite arsenic resistance and he and Vaucel, after treating a large number of patients, arrived in 1927 at the following conclusions

1 In the early stages of the disease tryparsamide was not satisfactory, relapses followed its use and parasites reappeared in the blood, and invasion of the central nervous system was not prevented

2 In the later stages, where there were definite indications of involvement of the central nervous system, much improvement was produced

3 In the early second stages, with a spinal fluid showing less than 70 lymphocytes per cmm and albumen under 0.5 gm. per litre, a large proportion (86.5 per cent) of successful results was obtained

4 In the later second stage, when the general state was good, even though the spinal fluid showed profound changes, much benefit resulted in 73 per cent

5 In the advanced second stage with clinical and general symptoms the results were 'successful' in 53 per cent, and another 15.6 per cent benefited

6 If some degree of improvement is not observed from the early injections nothing is gained by continuing the administration

Acetylarsen, or diethylamine acetarsol (acetarsol itself being acetylaminohydroxyphenylarsonate), rapidly expelled trypanosomes from the peripheral circulation, though this drug has the advantages of being well tolerated and not causing ocular disturbances, its effects unfortunately were not lasting, trypanosomes reappearing within three weeks. *Fourneau 270*, another of the phenylarsonic series, was employed by Ledentu and Waude in a 20 per cent solution freshly prepared and injected subcutaneously. They reported favourably upon its action in the second stage of the disease

Seeing that Bayer 205 benefited patients in the early stages and tryparsamide in the later, the suggestion was made and tested of combining the treatments in sequence. Thus, Maclean in Tanganyika reported in 1928, after two years' experience of the combined treatment and subsequent following up of cases for another three years, that the best procedure was giving Bayer 205 alone in the usual way and, after this course was completed, giving tryparsamide weekly in doses of 2-3 grammes, until at least 36 grammes had been given. A month was usually allowed to elapse between the termination of the first series (Bayer) and the beginning of the second (Tryparsamide) and, with some patients, a month was allowed to elapse after the fourth and after

the eighth injections. In other cases he gave a minimum of two injections of Bayer, each of 1 gramme, and then, after an interval of one or two months, twelve injections of tryparsamide, increasing the dose from 2 to 4 grammes, with the intervals as before. Maclean summarized his results as follows. He divided his cases into three classes, namely (i) Those with no appreciable wasting or œdema, that is early cases. Most of these recovered after treatment with Bayer alone. (ii) Those with œdema and wasting, but still able to be about and look after themselves, and (iii) The asthenic and emaciated, too ill to attend to their wants. Those belonging to these latter two classes nearly all died, but some in quite as bad a state recovered after receiving both drugs.

The following represents the opinion of those who have had long experience with these two drugs. Both produce immediate sterilization of the peripheral circulation in *gambiense* infections, Bayer certainly and tryparsamide very probably in *rhodesiense* infections also, together with definite physical improvement. The former, Bayer 205, has no influence on the meningeal reaction, that is, in the second stage the lymphocytosis and albumen content remain unaffected, and intrathecal injection of the drug is dangerous even in small doses, 0.2–0.3 gramme so given may be fatal. Tryparsamide, on the contrary, profoundly influences the meningeal reaction in *gambiense* infections. Bayer 205 is liable to cause a nephritis which may be fatal, while tryparsamide may give rise to visual disturbances and even blindness. In short

apart from the peripheral sterilizing action and the immediate physical improvement which it produced, Bayer 205 is useless in advanced cases of either *T. gambiense* or *T. rhodesiense* infection, in so far as it has no effect on the cerebrospinal infections and the disease proceeds to a fatal issue. For this class of case tryparsamide should undoubtedly be employed [W. Yorke].

Two other arsenicals must be mentioned, one which at the time (1925) seemed to meet some at least of the objections to the previous arsenical preparations, but is now no longer used, namely *novat-oxyd*, the sodium salt of paraphenyglycinamide arsenic acid, it produced rapid sterilization of the peripheral circulation and in most of the few chronic cases in which it was tried, the cell content of the spinal fluid was reduced, as was also the albumen, and improvement of the clinical state was observed.

The other drug is *neocryl*, of which Professor Warrington Yorke and his co-workers reported favourably to the Therapeutic Trials Committee in 1936. Neocryl is Sodium succinylmethylamid-p-arsenate. It proved less toxic than tryparsamide and possessed

greater trypanocidal power, a 15–20 per cent solution intravenously administered was well tolerated and the results were very good. Of eleven cases of human trypanosomiasis receiving a single course of this drug ten became clinically normal and the remaining patient improved.

We cannot leave the subject of treatment of this disease without reference to a method which in the early 'twenties of this century was much discussed and was known as Marshall and Vassallo's treatment by salvarsanized serum. This was carried out as follows. An intravenous injection of 0.6 gramme of neokharsivan was given and two hours later 60 c.c. of blood were withdrawn and set aside for twenty hours, serum separated from this, in quantity up to 20 c.c., was injected intrathecally after removal of a corresponding amount of cerebrospinal fluid. The authors claimed that this gave results "better than any hitherto obtained by repeated intravenous or subcutaneous injections of salvarsan, atoxyl, antimony or other preparations." This naturally drew the attention of all concerned in combating this terrible disease, and in September 1921 the *Lancet* announced that the Colonial Office had approved of a mission under Marshall and Vassallo's direction to investigate the serum treatment of human and animal trypanosomiasis.

As Yorke pointed out the same year, the work of Marshall and Vassallo is based on two fundamental assumptions: (1) Although the administration of one dose of salvarsan, neosalvarsan or atoxyl will sterilize the blood from trypanosomes, symptoms reappear in four months or so and the disease progresses to a fatal end. (2) This is due to the trypanosomes finding a protection in the central nervous system where the drug cannot attack them and whence they invade the blood again.

Warrington Yorke examines these in detail and shows that if not actually incorrect and unwarranted they must be considerably modified before they can be accepted, further, that the suggested method was not really new, but was substantially the same as that of Reichenow who tried it in 1914 and gave it up because the procedure did not sterilize the cerebrospinal fluid, and Marshall and Vassallo had not proved that it does by their method. Comparison of their results with those from other forms of treatment fails to substantiate their claim that their treatment surpasses previous methods (*Trop Dis Bulletin*, 1921, vol 18, pp 155–65).

The discussion went on for some years, but by 1926 the authors themselves were recording less success, of 214 so treated only twenty-five were alive and well after less than two years. The

reasons ascribed were that some had probably been reinfected, while others could not or did not respond because of heavy concomitant infestation with ankylostomes. For the last nine or ten years nothing more has been heard of this method of treatment.

During the past year or two a considerable number of publications has been issued which may be regarded as of a summarizing character and to which reference should be made for the information of those desiring to hear of certain points of a somewhat academic nature, but which may have subsequent wider application. First, there is C F M Swynnerton's monograph on the *Tsetse Flies of East Africa, a Study of their Ecology, with a View to their Control*, secondly, an Epidemiological Report issued by the League of Nations, written by H L Duke on *Recent Advances in the Biology of Trypanosomes of Sleeping Sickness*, in which he deals with factors which influence the development of Trypanosomes in *Glossina*, arsenic resistance, man's resistance to trypanosomes of the *brucei* group, the behaviour of man's trypanosomes in animals, and the origin of *T. rhodesiense*. He points out that human settlement in a game country must be protected from game tsetse, also that endemic sleeping sickness is a disease associated with poverty, inadequate food, poor physique, low resistance and standards of living—penalties attaching to life in the fly-country. Further, that if the standard of living of the native is improved and he is taught to apply the elements of sanitation the results already obtained in the Sudan, the Belgian Congo and Tanganyika will be attainable elsewhere.

We must remember that the opening up of the continent during the last thirty years or so [writes Duke] has facilitated the spread of human trypanosomiasis. Let us then acknowledge our obligations and vigorously continue the campaign until sleeping sickness is no longer a major scourge, or even a remote menace to man in Africa.

In conclusion it may be of interest to give a list of the principal dates and discoveries in connection with human trypanosomiasis in Africa.

- | | |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1734 | Atkins in <i>The Navy Surgeon</i> described negro lethargy which he had observed on the Guinea Coast three years before |
| 1803 | Winterbottom described the disease as he saw it in West Africa near Sierra Leone, and noticed that slave-dealers would not buy those with enlarged glands |
| (1846 | Trypanosomes first found, in fishes) |
| 1849 | Clarke observed the disease on the Gold Coast |
| 1869 | Guérin saw cases of negro lethargy in Martinique in slaves imported from Africa |

- (1879) Lewis found rat trypanosomes in Bombay)
- (1880) Evans found horse trypanosomes in Madras)
- 1890 Nepveu found trypanosomes in the blood of a man in Algeria,
while examining it for malaria parasites, but its significance
was not then known
- 1891 First case of sleeping sickness brought to London, under Sir
Stephen Mackenzie
- 1895 Bruce showed nagana to be due to a trypanosome, *T. brucei*
- 1900 Two cases of sleeping sickness in London under Patrick
Manson The pathology of these was studied by Mott
- 1901 Forde and Dutton found trypanosomes, *T. gambiense*, in the
blood of patients in the Gambia
- 1902 First Royal Society Sleeping Sickness Commission
- 1902-03 Castellani saw trypanosomes in the cerebrospinal fluid of
patients in Uganda
- 1903-06 Second Royal Society Sleeping Sickness Commission
- 1903 Bruce and Nabarro showed that trypanosomiasis was spread
by *G. palpalis*
- 1905 Wolferstan Thomas introduced atoxyl in treatment
- 1906-07 German East African Sleeping Sickness Commission
- 1906-08 French Congo Sleeping Sickness Commission
- 1907-08 Foreign Office (British) International Sleeping Sickness Con-
ference
- 1908 Sleeping Sickness Bureau established in London
- 1908 Third Royal Society Sleeping Sickness Commission
- 1908 Plimmer and Thomas introduced tartar emetic for trypano-
somiasis (Livingstone, half a century before, had given
arsenic to horses for nagana)
- 1908-10 Togoland Sleeping Sickness Commission
- 1909 Spanish Sleeping Sickness Commission on Gulf of Guinea
- 1910 New species of trypanosome, *T. rhodesiense*, reported by
Stephens and Fantham
- 1910-12 Belgian Sleeping Sickness Mission to Katanga
- 1911 Expedition of the Liverpool School of Tropical Medicine to
the Gambia
- 1911 Luangwa Sleeping Sickness Commission of the British South
Africa Company
- 1911 Fourth Royal Society Commission, to Nyasaland
- 1912 Yorke and Kinghorn showed that *G. morsitans* was the trans-
mitter of *T. rhodesiense*
- 1912 The Sleeping Sickness Bureau becomes the Tropical Diseases
Bureau
- 1925 First International Sleeping Sickness Conference, under the
auspices of the League of Nations, met in London, 19th-22nd
May
- 1926 The Tropical Diseases Bureau becomes The Bureau of Hygiene
and Tropical Diseases
- 1928 Second International Sleeping Sickness Conference, under the
auspices of the League of Nations, met in Paris, 5th-7th
November
- 1933 Conference on Trypanosomiasis (Animal and Human) Re-
search, held at Entebbe, Uganda, in November

- 1934 Governors' Conference on Co-ordination of Research, held at Nairobi, in May
- 1935 Closing down of the Human Trypanosomiasis Institute, Entebbe, Uganda, 31st December (but research still to be carried on there)
- 1936 Conference of Governors of East African Territories met at Entebbe, Uganda, 29th-31st January, to discuss co ordination of research on Tsetse Fly and Trypanosomiasis

AMERICAN TRYPANOSOMIASIS

The human trypanosomiasis which is met with in South America has been called American sleeping sickness on the analogy of the African disease. The term, however, is a bad one for lethargy, the characteristic of the later stages of the infection in Africa, is not a symptom, certainly not a common symptom, of the American disease. A better designation is American Trypanosomiasis or Chagas' disease, after Carlos Chagas of Rio de Janeiro, who first discovered and described the condition, and described it, moreover, so fully that subsequent investigators have had little to do beyond lining in, shading and intensifying the original picture. Chagas gave, as we shall see, if anything rather too full an account, ascribing to the disease certain symptoms which are probably not a true part of the infection, in this respect, subsequent investigators have had to modify the original picture. The determination of the essentials—the cause, the transmitting agent, the mode of transmission, the symptoms, and so forth—was the work of one man, Chagas, and he has well earned the honour, if honour it be, of having the disease named after him.

In 1907 a railway was under construction in the northern part of the Province of Minas Geraes, Brazil. Malaria was very prevalent there and Carlos Chagas was commissioned to investigate the reasons and organize measures to deal with it. While engaged on this work he heard of the *barbeiro*, a biting Reduviid bug, living in the dwellings of the people, especially of the poor, hiding in cracks and crevices in walls and ceilings during the day, but as soon as it became dark and lights were extinguished they emerged to bite the occupants, often on the face. If a light was struck they would be seen scuttling to their hiding-places. They usually leave a house abandoned by human beings. These bugs are about an inch and a quarter in length, the female larger than the male. It belongs to the genus *Conorrhinus*. Darwin, in his *Naturalist's Voyage*, on the researches made during the voyage of H.M.S. *Beagle*, refers to this or an allied species in these words

At night I experienced an attack (for it deserves no less a name) of the *Benchuca*, a species of *Reduvius*, the great black bug of the Pampas. It is most disgusting to feel soft, wingless insects, about an inch long, crawling over one's body. Before sucking they are quite thin, but afterwards they become round and bloated with blood, and in this state are easily crushed. One which I caught at Iquiqui (for they are found in Chile and Peru) was very empty. When placed on a table, and though surrounded by people, if a finger was presented, the bold insect would immediately protrude its sucker, make a charge and, if allowed, draw blood. No pain was caused by the wound. It was curious to watch its body during the act of sucking, as in less than ten minutes it changed from being as flat as a wafer to a globular form. This one feast, for which the *Benchuca* was indebted to one of the officers, kept it fat during four whole months, but after the first fortnight, it was quite ready to have another suck.

Chagas examined some specimens of this *Conorrhinus* and found crithidial flagellates in large numbers in the hind-gut. Some of these infected bugs were sent to Oswaldo Cruz who allowed them to bite a marmoset, *Callithrix (Hapale) penicillata*, and in the blood of the monkey, three to four weeks later, numerous trypanosomes were found which differed morphologically from those previously recorded. Other laboratory animals proved to be experimentally susceptible, other monkeys, guinea-pigs, rabbits, and, to a less degree, dogs, especially adult dogs, puppies were fairly easily infected. Subsequently evidence was adduced to show that several species of armadillo were reservoir hosts. When the parasite was first found there was natural uncertainty as to whether it had any pathogenic importance, either for animals or man.

The trypanosome proved readily cultivable on N N N medium, and further study showed Chagas that an uncertain percentage of specimens of *Conorrhinus* from houses in the infested region was infective to vertebrates, also that larvæ reared in the laboratory and allowed to feed on infected animals are not always themselves capable of transmitting infection even though flagellates are visible in the mid-gut, but those which do become infective attain that state eight to ten days after their infective feed.

He found by further animal experiment that infection rate *via* the bug was higher than that obtained by blood inoculation, for example, guinea-pigs infected by the bug died in five to ten days, whereas after blood-inoculation they might survive for as long as two months. The question of the pathological processes will be spoken of later, but we may state here, as arising out of this experimental work, that when death occurred after the animal had been infected by the bite of *Conorrhinus* few, perhaps no,

parasites might be discoverable in the peripheral blood, but active schizogony might be observed in the pulmonary capillaries, and some of the animals suffered from keratitis as a complication and this might be severe enough to cause blindness

There was need to use only laboratory-bred bugs because nearly all those caught in houses were harbouring parasites in their mid-gut and, of course, these might be natural flagellate infections or commensals having nothing to do with the trypanosome of Cruz. A somewhat curious fact was noted, namely that the bug readily acquired infection from an infected monkey, but not from a guinea-pig although the guinea-pig was easily infected by the bug

Search for the habitat of the Reduviid revealed it hiding not only in the dwellings occupied by man but also in outbuildings, stores, stables, coach-houses, hen-runs, etc. Although, as a rule, it attacked by night nevertheless if a man leaned against a wall they might come out and attack him at any time, even in daylight. Its bite, as Darwin noted, seemed to cause no pain, in fact, a child asleep might be bitten repeatedly and not awaken

Two processes of development of the trypanosome could be observed in the insect (1) Sexual, requiring eight days to reach the stage of transmissibility (2) Asexual, simple multiplication, as in artificial cultures, leading to crithidial forms in large numbers in the hind-gut

A few words on the name of the parasitic flagellate. Chagas at first classed it as a trypanosome, later, when he observed in the tissues leishmania forms, he concluded that development took place by schizogony and he created a new genus which he denominated *Schizotrypanum* and for long the name *Schizotrypanum cruzi* was used, and is even now by some writers. Since, however, multiplication occurs by the usual method of binary fission, there is no valid reason for removing it from the genus *Trypanosoma* and the name more generally used is *Trypanosoma cruzi*. Further, according to Hoare, the flagellate forms seen in the lungs belonged not to this organism but to *Pneumocystis carinii*.

The Reduviid first studied by Chagas, *Conorrhinus megistus* or *Triatoma megista*, is not the only vector. In other parts where the disease which it causes exists (this will be dealt with later) the *T. megista* is not found, in Venezuela, for example, the transmitter is *Rhodnius prolixus*, and even where other Reduviids exist—there are four species in Venezuela, namely, *Eutriatoma maculata*, *Panstrongylus geniculatus* and *Spiniger rubropictus*, in addition *R. prolixus*—this is the only one found infected in nature. It can

transmit infection in all three stages, as larva, as nymph and as imago

We may anticipate the chronological order of events and speak here of the method of transmission of infection. Although more than a quarter of a century has elapsed since Chagas first described the vector and the disease to which it gave rise, the actual method of transmission in nature is still undetermined.

We may dismiss with passing mention as a rarity the fact that Nattan Larrier in 1913 found that *Trypanosoma cruzi* might be seen in the milk of women experimentally infected, and the case, recently described by Salvador Mazza and his fellow-workers, of a woman living in Makallé, Chaco, who in January 1936 showed symptoms of the disease. In March she had a child and ten days later left for Resistencia (Corrientes) where the mother and child have lived since that time. The infant's blood was examined when they left Makallé and no parasites were found. Eleven weeks later, after an attack of diarrhoea associated with slight adenitis (to the size of maize grains) at the occiput and neck, axillæ and groins, enlarged liver and spleen, the child's blood was found to contain trypanosomes in numbers (the vector of *T. cruzi* is not present in Resistencia) and the mother's milk contained them, though none was seen in her blood, even by the thick-drop method of examination.

Chagas originally held that the first stages of development of the infecting parasite took place in the salivary glands of the vector and that infection was transmitted by its bite. Brumpt, however, was of the opinion that the life-cycle was completed in the hind-gut and that infection was brought about by faecal contamination of the wound made by the bite, either by the rubbing caused by the irritation or orally. His conclusions being based on exact objective observation and experiment (C. A. Hoare) have received wide-spread recognition, but at the same time the notion of infection by bite has not been altogether given up. Dias carried out further experimental work at the Oswaldo Cruz Institute, Brazil, and thereby confirmed the findings of Brumpt. He was unable to get laboratory animals infected by the bite, but invariably succeeded by faecal contamination.

As long ago as 1913 E. Brumpt and Gonzalea-Lugo found the trypanosomes in *R. prolixus* more than two months after the bug had fed on an infected monkey. If this insect maintains infection indefinitely it is probably a more dangerous vector than is *Triatoma megista*, for the latter does not defæcate for some seconds, even some minutes, after feeding, whereas the former does so immed-

ately after withdrawing its proboscis, hence rubbing the spot bitten would in the latter case give more chance, more likelihood, of infection

Under experimental conditions, but not in nature, *Trypanosoma cruzi* can develop in *Cimex* and *Ornithodoros*

The natural transmitters are widely distributed in America between 35° South latitude and 30° North. They are found all over the south-east parts of Brazil and Uruguay, except the coastal region, in Paraguay, in all the Provinces of northern Argentina, in Chile, Peru, Venezuela, Panama, Salvador, Guatemala, and as far up as southern California and Arizona

We will now retrace our steps and return to the early discovery of the parasite by Chagas in human subjects. As stated at the beginning of this chapter the object of Chagas' visit to Minas Geraes was to study the prevalence of malaria there, to ascertain the reason for it and suggest and advise measures of control. On his proceeding to examine the blood of the inhabitants, and particularly that of the children, he found the trypanosomes and those harbouring them presented symptoms of marked anæmia, stunted growth, delayed development even to actual infantilism, œdema, localized in some, general in others, enlargement of lymphatic glands—cervical, axillary, inguinal, femoral—and nervous disorders ranging up to actual imbecility, many were febrile and had palpable livers and spleens. In a certain proportion he observed goitre. Death occurred in acute cases with convulsions, in some with syncope, in some with general œdema, like that of severe ankylostomiasis or beriberi. In very acute cases with cerebral symptoms the numbers of parasites in the peripheral blood increased till death.

In others, symptoms were strangely wanting, a history might be elicited of previous mild fever (in others the temperature might rise to 104° F) with swelling of the face or eyelids and swollen glands. This facial œdema was a fairly constant early sign and the glandular enlargement might then be pre-auricular, sub-maxillary or cervical. In a large proportion the more acute symptoms might subside in a month or so and the condition pass into a chronic disease. In these the trypanosomes would decrease until they could no longer be found in the peripheral blood.

Locally, the disease went by the name *opilação* or *cangany*, the former is a name given elsewhere to hookworm infestation and the anæmia and œdema associated therewith, but in the cases

described by Chagas these symptoms occurred in the absence of ankylostomes

Inoculation of the blood of children so injected into marmosets or guinea-pigs set up disease in these animals. In the former trypanosomes would appear in the blood some eight days later, many of the animals died on the sixth day and developmental stages (leishmania-like bodies) would be found in the lungs.

Chagas was not, it appears, the first to record trypanosomes in human beings in South America. In 1904 Lacerda reported finding them in films from the spinal cord of a patient dying from beriberi [so it is recorded] and he regarded the trypanosome as the cause of the beriberi. It is open to conjecture that this may have been a case of anasarca due to trypanosomiasis—'Chagas' disease' before Chagas—and not beriberi at all.

It has been stated above that acute symptoms would in many cases subside and the disease pass into a chronic stage. These chronic cases Chagas subdivided into five clinical groups

- 1 Pseudomyxoedematous, more often seen in the young, under fifteen years, often accompanied by bronzing of the skin, ascribed to adrenal affection, with perhaps some thyroid involvement

- 2 Myxoedematous

- 3 Cardiac, with irregularity of action, extra-systoles, sinus arrhythmia, etc., and at autopsy parasites in leishmanial form might be seen in the myocardium

- 4 Nervous, with various forms and degrees of paralysis, aphasia, idiocy. In children associated with arrest of bodily development

- 5 Chronic type with intermittent exacerbation of symptoms. In these cases Chagas laid much stress on the presence of goitre

It seems peculiar that with a vector so widely distributed as has been referred to above the actual number of human cases recorded is strangely small. Most have been reported from Minas Geraes where it was first seen, next most in São Paulo. By 1937 Warrington Yorke could collect records of only 113 cases (see Table), but Salvador Mazza in July of the same year, writing in *Prensa Médica Argentina*, contributes a "note on 240 [241] acute cases in the Argentine" distributed as follows. In the Western districts: Mendoza 67, Catamarca 12, La Rioja 10, San Juan 7, Ninquén 1—a total of 97, in the Central region: Tucumán 6, Córdoba 3, in the Northern provinces: Santiago del Estero 27, Chaco 26, Jujuy 16, Salta 9, Formosa 6—together 84, and in the Littoral States: Santa Fé 46, Corrientes 3, Entre Ríos 2—together 51. These are cases known to the M E P R A (Misión de Estudios de Patología Regional Argentina), others doubtless occur but are not reported to the Misión.

Table showing the geographical distribution of individuals in whom *T. CRUZI* has been found

Country and Province	No of cases described	Authority	Age and sex
<i>Brazil</i> Minas Geraes	Many	Chagas (1916) Villela and Bicalho (1923) Villela (1930), Dias (1934), etc	29 cases children mostly under 2 years Many cases
São Paulo	4	Carini and Maciel (1914) Villela (1918) Bayma (1914)	1 case ♀ 10 years 1 case child 2 cases child and adult
<i>Venezuela</i> Guárico	4	Tejera (1919) Torrealba (1934)	3 cases ♂ 9 months, ♂ 2 years†, ♀ 17 years 1 case, ♀ child
<i>Salvador</i>	2	Segovia and Hurtado (1914)	2 cases ♀ 30 years, ♂ 45 years
<i>Peru</i>	2	Escomel (1919) Noguchi (1924)	1 case ♂ 40 years 1 case <i>T. cruzi</i> found in blood culture from sup posed case of yellow fever
<i>Guatemala</i>	3	Reichenow (1934)	3 cases ♀ 14 months, ♂ 14 months, ♂ 18 months
<i>Panama</i>	19	Miller (1931) Clark and Dunn (1932) Clark (1934) Personal communication to De Coursey DeCoursey (1935) Johnson and DeRivas (1936)	3 cases ♀ 18 months, ♀ 2 years, ♂ 6 months 2 cases ♂ child, ♀ 10 years 7 cases 6 years, 36 years, 10 years, 25 years, 50 years, 18 years, 74 years 1 case 3½ months† 6 cases ♂ 3 months†, ♂ 3 years†, ♀ 14 years, ♂ 1½ years, 28 years, 14 years
<i>Argentina</i> Catamarca	12	Geoghegan (1928) Geoghegan (1929) Geoghegan (1933) Mazza and Ruchelli (1934) Mazza and Ruchelli (1936)* Mazza and Herera (1936)*	2 cases, 9 months, child 1 case ♂ 7 months† 2 cases, ♂ 3½ months, ♂ 8 months 2 cases ♀ 5 years, ♀ 9 years 4 cases ♀ 7 years, ♂ 2 years, ♂ 2½ years, ♀ 32 years 1 case ♂ 35 years
Chaco	7	Romano (1934) Mazza and Govi (1935) Mazza and Palamede (1936) Mazza and Valle (1936) Mazza and Corsi (1936) Mazza and Corsi (1936)*	1 case ♀ 2½ years 1 case ♂ 4 years 1 case ♂ 1½ years 1 case ♀ 6 months 1 case ♂ 3 years 2 cases ♀ 11 years, ♂ 2 years

Country and Province	No of cases described	Authority	Age and sex
Córdoba	5	Zuccarini and Oyarzabal (1933) Villegas (1934) Mazza and Sanchez (1936)*	1 case ♂ 8 years 2 cases ♀ 23 years, ♀ 3 years 1 case ♂ 6 years
Corrientes	2	Mazza, Benítez and Janz (1936) Mazza and Benítez (1936)	1 case ♀ 6 years 1 case ♂ 18 years
Entre Ríos	2	Caceres and Izaguirre (1935) Mazza, Idelsohn and Parcerisà (1936)	1 case ♂ 5 years 1 case ♀ 3 years
Formoso	1	Mazza (1936)	1 case ♂ 4 years
Jujuy	12	Muhlens, Dios, Petrocchi and Zuccarini (1925) Mazza (1926) Mazza (1934) Mazza and Almaráz (1934) Mazza (1934) Mazza (1936)* Mazza (1936)* Mazza (1936)* Mazza and Chacon (1936)*	1 case ♀ 8 years 1 case ♀ 27 years 2 cases ♂ 4 years, ♀ 6 months 1 case ♀ 5 years 1 case adult 1 case ♀ 2 years 3 cases ♂ 1½ years, ♂ 7 years, ♀ 8 years 1 case ♀ 35 years 1 case ♂ 3 years
La Rioja	1	Fitte (1935) Mazza and Catolan (1936)*	1 case ♂ 1½ years
Mendoza	3	Mazza, Germinal and Basso (1935) Basso, G. and Basso, R. (1936)*	1 case ♀ 9 months 2 cases ♂ 9 years, ♂ 4 years
Salta	3	Niño (1928) Mazza and Mamoli (1936) Mazza and Cornejo (1936)*	1 case ♀ 38 years 1 case ♂ 4 years 1 case ♂ 37 years
San Juan	2	Mazza and Nasti de Fischer (1935)	2 cases ♀ 6 years, ♀ 11 months†
Santa Fé	20	Romaña (1934) Mazza and Romaña (1934) Romaña (1934) Mazza, Romaña and Parma (1935) Romaña (1935) Mazza, Romaña and Parma (1936) Mazza, Romaña and Zambra (1936) Mazza and Schreiber (1936)*	1 case ♂ 8 years 1 case ♀ 1 year† 3 cases ♂ 1½ years, ♂ 10 years, ♀ 4 years 1 case ♂ 2½ years† 2 cases ♂ 9 years, ♂ 4 years 1 case ♂ 8 years 1 case ♂ 7 years 3 cases ♀ 6 years, ♀ 7 years, ♂ 2½ years

Country and Province	No of cases described	Authority	Age and sex
Santiago del Estero	10	Romaña and Klemensiewicz (1936)*	2 cases ♂ 12 years, ♀ 2 years
		Romaña (1936)*	4 cases ♂ 52 days, ♀ 7 years, ♂ 4 years, ♂ 12 years†
		Romaña and Cereijo (1936)*	1 case ♀ 5 years
		Mazza and Guerrini (1934)	2 cases ♀ 4 years, ♀ 14 years
		Raimondi and Feijoó (1934)	1 case ♂ 8 years
		Mazza and Olle (1936)	2 cases ♀ 5 years, ♂ 33 years
Tucumán	3	Feijoó (1936)	2 cases ♂ 19 years, ♂ 26 days
		Mazza and Guerrini (1936)*	1 case ♀ 7 years
		Mazza and Argañaráz (1936)*	2 cases ♀ 3 months, ♂ 8 months
		Muhlen, Dios, Petrocchi and Zuccarini (1925)	1 case ♀ 5 months
		Dios, Zuccarini and Oyarzabal (1925)	1 case ♂ 4 years
		Borzone and Coda (1925)	1 case child

* The references marked thus relate to papers which are to be found in Novena Reunión Pat Reg Soc Argentina

† The cases marked thus ended fatally

NB—In a recent article Mazza (1936c) states that the total number of infected cases found by the Misión de Estudios de Patología Regional Argentina between 1932 and 1st August, 1936 is 109. Some of these cases have not yet been recorded. These 109 cases were distributed as follows—Entre Ríos 2, Corrientes 2, Santa Fé 27, Formoso 1, Chaco 10, Santiago del Estero 14, Salta 4, Jujuy 10, Córdoba 2, Catamarca 10, La Rioja 3, San Juan 2, and Mendoza 22. The total number of deaths observed among these cases is 7, viz, 4 in Santa Fé, 1 in Santiago del Estero, 1 in San Juan and 1 in Mendoza.

The following sums up the general belief regarding the chief points as the results of Chagas' work

In Brazil the principal insect vector is *Triatoma megista*, which is present in large numbers in dwellings and feeds on man during the night. It usually attacks the face and lips of sleepers, for which reason it is named *barbeiro* or the barber, or 'kissing bug'. They defæcate soon after feeding (Rhodnius sooner than Triatoma). They are commonly found in the beds of the inhabitants in endemic districts and the bedding is usually soiled with the excreta of the insects and blood and spots from their being crushed. It is conceivable that human infection results from the droppings contaminating the mucous membrane of the mouth, nose or eyes, or from their being rubbed into the skin by scratching.

Let us consider in a little more detail two or three of the symptoms, for, as regards one at least—the goitre—there has been

much discussion and opinion has veered round so that this, on which Chagas laid no little stress, is not believed now to be an essential part of the symptomatology

First, the localized swelling of the eyelids and the adjacent tissues, known as Romaña's sign, has come of late years to be regarded as almost a pathognomonic early sign. It is the result of the bite of the insect being so often on the face near the eye and rubbing of the spot and introducing the faeces with the contained parasites. In places where the disease is endemic this sign, which as stated is usually early, should indicate search for further proof of trypanosomiasis.

Next, the cardiac symptoms. Patients presenting heart disease in various forms appear from all accounts to be of more than usual frequency in South America, cases of unexplained bradycardia, of extra-systoles, heart-block, cardiac dyspnoea, syncope and sudden death are unusually common. Thus, in the Province of Santa Fé, in one district 5 out of 40, in another 20 out of 228 total deaths were due to syncope. Hitherto many of these have been ascribed to syphilis, some of them have during life given a positive Wassermann or Kahn reaction, others have not. Examination of the latter has shown leishmanial forms of *T. cruzi* in the myocardium, and if the former be also examined microscopically in some of them the parasite is seen there too. Now, with more modern methods of diagnosis this would probably be discoverable during life (see below). The present state of knowledge regarding the relationship of infection by *T. cruzi* and myocardial disease may be epitomized as follows

- 1 Cases of chronic heart disease are very common in many parts of South America where infected bugs and cases of human trypanosomiasis are known to occur, and syncope accounts for a high percentage of the deaths

- 2 *T. cruzi* is known to have a predilection for the myocardium

- 3 In a number of these cases trypanosomes are found in the peripheral blood, but we must guard against interpreting coincident presence with consequential effect

- 4 If the cardiac lesions so common in endemic regions are not due to the trypanosome, we are ignorant of the cause

As Warrington Yorke states

There seems on the whole to be a *prima facie* case that American trypanosomiasis may actually be responsible for a good deal of the heart disease which is apparently so common in certain endemic areas in Brazil, Uruguay and the Argentine, and the cause of so many early deaths. The chronic cardiac form of the disease may be a sequel to an acute infection in infancy or the consequence of repeated infection

in later life If this should eventually prove to be the case, the American trypanosomiasis will indeed assume a pathological significance of the first magnitude The subject is obviously one which urgently requires much further work To reach a final conclusion will be a matter of no small difficulty, and probably the most fruitful line of investigation will prove to be the careful observation of cases of the acute infections in childhood, with adequate post-mortem examination of the fatal cases, and prolonged observation extending over many years of those which survive the acute attack, with the object of ascertaining whether they subsequently develop the characteristic cardiac manifestations Such subsequent observation will necessarily involve repeated examination for the trypanosomal infection, the response to the Machado reaction, should this prove to be of real value as a test for the infection, and the observation of syphilis and other infections and infestations which might conceivably give rise to chronic myocardial change

Lastly, the question of thyroid affections and Chagas' disease When Chagas was carrying out his early investigations he found many of the patients had enlarged thyroids, he regarded these as examples of a special form of the disease and wrote of it under the title *Thyreoidite parasitaria* As we have already seen two of Chagas' five clinical groups were pseudomyxœdematous and myxœdematous

Probably among the first to raise doubts of this were R. Kraus, F. Rosenbusch and C. Maggio who, in 1915, when discussing goitre, cretinism and Chagas' disease, stated that in some districts of the Argentine between 60 and 70 per cent of the population suffered (and suffer now) from goitre and that there was need for study of the disease in provinces where there is no endemic goitre but where infected bugs are found, and to determine whether there are patients there presenting the symptom-complex of the disease Two years later Kraus and Rosenbusch noted, first, that in the mountainous regions of the Argentine *Triatoma* infected with *T. cruzi* is found, and in some parts goitre and cretinism occur which differ in no essential from classical cases of these conditions Secondly, that in other parts of the same regions, in the Calchaquí Valley for instance, many infected insects could be found but no persons suffering from goitre or cretinism The same holds good also in Buenos Aires and Córdoba Doubts continued to be expressed and in 1923 we find Gustavo Lessa observing that myxœdema is a constant feature in acute cases of the disease and that the domiciliary distribution of the *Triatoma* is the same as that of goitre, but that there was as yet no proof that the relation was causal This, it will be seen, is at variance with the statements of Kraus and Rosenbusch, and is, in fact, not correct The distribution of human infection with *T. cruzi* in the Argentine

does not exactly coincide with that of goitre and cretinism, the former is found in places where the latter is not. The same year, 1923, the National Academy of Medicine of Brazil appointed a Commission to study this question and a report was issued in 1924. This was of the nature of a polemical publication, containing the views of the Commission and Chagas' replies, but left the main question unsettled. In 1926 Kraus returned to the fray, he repeated his former convictions and the reasons therefor and added that from the clinical aspect it is difficult to distinguish endemic goitre and cretinism from the clinical picture of the acute and chronic infections depicted by Chagas. According to Munk, in the district where Chagas made his discovery 75 per cent of the people had goitre and every family its dwarf, cretin or paralytic. A further difficulty arises in that the trypanosomes are no longer found in the blood in chronic cases. Chagas' disease and endemic goitre undoubtedly overlap in their distribution, and the point was again stressed that there was need to search for cases of trypanosomiasis in Brazil or the Argentine in places free from goitre but where infected *Triatoma* are present. This Kraus and Rosenbusch had already done and reported upon in 1917 (see above).

In 1929 appeared a large work in Portuguese, by Flavio L Niño, well illustrated, dealing with the whole subject—the parasite, its vectors, the clinical symptoms, pathology and epidemiology. From this we hoped and expected to learn much and to have a reasoned argument for or against the ætiological connection between thyroid conditions and American trypanosomiasis, but study of his work leaves us in this respect unsatisfied. Niño divides patients clinically into three main groups, with subdivisions, namely

- I Acute, with trypanosomes in the peripheral blood
 - (a) With encephalo-myelitis
 - (b) Without encephalo-myelitis
- II Chronic, in whom trypanosomes are not found in the peripheral blood
 - (a) Pseudomyxœdematous
 - (b) Myxœdematous
 - (c) Cardiac
 - (d) Nervous
- III 'Metatrypanoidal phenomena'—goitre, cretinism, infantilism

It will be seen that he follows closely the earlier classification of Chagas and in the last rather begs the question, and he concludes, not very helpfully,

The coincidence of the goitrous zone and that of American trypanosomiasis and the constancy of thyroid enlargement in the children attacked, and the histological findings lead to the conclusion that this is a form of Chagas' disease

In 1935 there appeared a more able summing-up of the question by Cecilio Romãna in an article entitled *Trypanosomiasis americana y bocio endemico*. He quotes Chagas' description of the disease and the reasons which led him to conclude that the goitre present was of trypanosomal origin and sums up the evidence in the following points

Pro

- (i) Myxœdema is often found in the acute cases and in the later stages the thyroid is enlarged and trypanosomes are present
- (ii) Thyroid enlargement is common in regions where the disease was first studied (Northern Minas Geraes) and where other forms of the disease exist
- (iii) The infectious theory of the goitre has been widely accepted by those who have specially studied the condition and they are agreed that "the goitre found in regions where Chagas' disease prevails is caused by the latter" [The reasons for this not being given the argument loses all force, except as an *ipse dixit*]
- (iv) That intra-uterine infection by trypanosomes would account for the congenital goitre and that observed in children living in districts where Chagas' disease prevails [no evidence of intra uterine infection is adduced]

Contra

- (i) The myxœdema present is found in human beings and even in animals who show no [other] evidence of trypanosome infection
- (ii) There are regions in Brazil and the Argentine where the two coexist, or are superposed, and others where goitre has been known for a long time, but where Chagas' disease is not met with
- (iii) There are areas where the trypanosomiasis, both in acute and chronic stages, is present, but goitre is not observed
- (iv) The pathology of the goitres associated with the trypanosome infection has not been studied till recently except in chronic cases of Chagas' disease, and even now nothing characteristic has been found to differentiate them from endemic goitre in other parts of the world
- (v) Much experimental work has been done, but thyroid hypertrophy has not been produced nor has the parasite shown any predilection to affect the thyroid gland

The same year, 1935, Evandro Chagas, a son of Carlos Chagas, who has made this disease a subject of intensive study, in a general review of it writes

That the disease occurs in goitrous districts is known, but the older idea that there was a goitrous form of the disease is no longer main

tained Up to the present time there has been no experimental work confirmatory of Carlos Chagas' theory that the goitre occurring in these regions is due to infection by *Trypanosoma cruzi*

Little need be said regarding the pathology of this disease, for it is of historical interest only in so far that Chagas, having seen division forms in the lungs, was led to consider this as the only method of multiplication and to suggest on that account a new zoological genus, *Schizotrypanum*, for the parasite Vianna found them in the tissues, the myocardium and the striped muscles, in 1911, and having the same morphology as in cultures Torres in 1917, described more minutely the cardiac lesions The 'parasitic thyreoiditis' of Chagas we need not refer to again Recently, in 1937, it has been shown that the dacryo-adenitis, an early symptom of the disease (and together with the swelling of the eyelids now going under the name of Romaña's sign, a useful diagnostic indication in the early stage) is associated with leishmania forms in the granulations over the lower tarsal conjunctiva

The question of diagnosis has historical importance In the earliest days this had to be made on the clinical symptoms, confirmed by finding the trypanosome in the blood The unilateral facial oedema was a valuable sign, since it appears early, from the sixth day, whereas the trypanosome was not found by direct smear till some ten days later This symptom has been studied more carefully of late and now goes by the name of *Conjunctivitis schizotrypanósica unilateral* in the Argentine and is characterized by starting abruptly with swelling of lids and conjunctiva, and slowly subsiding, by painless oedema, often of a reddish-violet colour, marked injection to actual chemosis of the conjunctiva, the swelling extending over the face, corneal affection is absent but the pre-auricular, parotid or submaxillary gland of the same side is usually enlarged

Except in the early or acute stages the trypanosomes might escape detection in smears of the peripheral blood and, if scanty, their presence might be proved by animal inoculation, 5-10 c c of the blood being injected into guinea-pigs or puppies For this disease this method was first used by Bayma, and Carini and Maciel in 1914, and afterwards by Tejera (1919), Niño (1928), Torres (1930) and several since then Brumpt's method of *xenodiagnosis*—allowing a clean arthropod transmitter to feed on the suspected patient and subsequently observing whether the insect becomes infected—was tried with success by Torres in 1915 and later by Torrealba, Dias, and Romaña Care must be exercised,

says Yorke, when speaking of this, because bugs can infect each other by coprophagy

Lastly, we have the *Machado reaction*, devised by Machado and Guerreiro in 1913 for diagnosis of the disease in chronic form, when trypanosomes are not found in the blood. For this a glycerin and water extract of the heart or spleen of infected puppies is used. The results are quite independent of the Wassermann reaction, for normal tissues do not serve for it. Many have reported on its usefulness—Lacorte in the Lassance Hospital, Minas Geraes in 1927, Villela in 1930 who tested it in various parts of the State, and Mazza in 1934 in the State of Jujuy. Evandro Chagas noted that the sera of persons who had had the disease and had left the endemic area as long as fifteen years still gave a positive Machado reaction. Kelser in 1936 modified the original method by utilizing artificial cultures of *T. cruzi*, because he found that antigens made with the tissues (heart or spleen) of infected animals differed widely in activity.

If further study and more extensive testing should confirm its specificity the reaction should prove of immense value, not merely in the diagnosis of cases, like the Wassermann reaction for syphilis, but epidemiologically, as the mouse-protection test in mapping out yellow fever areas. Then, instead of the small number of cases, surprisingly small considering the extensive prevalence of the vectors, it may be found that American trypanosomiasis is responsible for much sickness in South America. At present the distribution of *Triatoma* is very wide. Dios, de Sommerville, Bonacci and Aldao in 1936 examined over 30,000 of them in 340 localities in 158 departments of 13 provinces, namely, Catamarca, Córdoba, Corrientes, Entre Ríos, Jujuy, La Rioja, Mendoza, Salta, San Juan, San Luis, Santa Fé, Santiago del Estero and Tucumán, and in 32 localities in the territories of Chaco, Formosa, La Pampa, Misiones, Neuguen and Rio Negro. 74.1 per cent of the localities were found infected with the *Triatoma* and 7.7 per cent of the bugs were infected with trypanosomes. If, therefore, infected *Triatoma* is presumptive evidence that human infection may occur, or may be expected to occur, the significance of these findings can hardly be over-estimated. It may be that the infection is not naturally one of man but of animals, man becoming, as it were, incidentally attacked, we see an analogy in plague, a disease of rats primarily, in tularæmia, a disease of various rodents. So American trypanosomiasis is found spontaneously in certain reservoir hosts showing no clinical signs of infection in domestic animals, the dog and cat, in several species of armadillo, *Chaet-*

phiacus vellerosus vellerosus, the long-haired armadillo (Mazza *et al* 1930), *Dasypus novemcinctus*, the nine-banded armadillo (Mazza 1930), *Zædyus pichy caurinus* (Mazza 1935), the weasel or opossum, *Didelphis paraguayensis*, and *Lutreola crassicaudata* (Mazza *et al* 1931), the fox, *Pseudolapex culpæus* (1935), and the ferret, *Grissonella vatellina* (1935)

Finally, on the subject of treatment there is little, in fact nothing, to be said. The drugs which have proved beneficial and trypanocidal in African trypanosomiasis have been tried without effect. Evandro Chagas sums up the matter by saying that there is no specific treatment known at present, *i e* in 1935. He writes:

Não existe, até ao presente momento, tratamento específico para a tripanosomíase americana. Medicamentos de acção tripanosomícida têm sido experimentados por numerosos pesquisadores sem qualquer êxito (*Memorias Inst Oswaldo Cruz* 1935, V 30, No 3)

CHAPTER IX

LEISHMANIASIS

KALA AZAR

I EARLY VIEWS OF ITS NATURE

Kala azar, or Black Fever, has, it is believed, existed for centuries, it was certainly rife in Bengal and Assam long before its nature was recognized. Though it was known to have a fairly wide distribution—Bengal, Assam, North China, the Caspian region, the Mediterranean littoral, Anglo-Egyptian Sudan, Mesopotamia, Sumatra, Siam, and the Lake Chad district—towards the end of last century its area of endemicity was, or at least was thought to be, limited and in consequence it did not obtain the attention it deserved. It was not until 1910 that Aspland showed the disease to be widespread in Northern China, and the following year Cochrane reported cases elsewhere in that country. Saville found it in Tientsin, Jerusalem in the Hoang Ho district, and Jefferys and Maxwell recorded its presence in Formosa.

Before modern methods of treatment came into vogue its fatality rate was very high, in the neighbourhood of 90 per cent, it caused a long and lingering fever and in places, Nowgong for example, reduced the population enormously. In some villages two-thirds of the inhabitants might succumb, the land consequently had to be left uncultivated and became almost valueless, and labour on some tea estates towards the end of last century was so heavily involved that many gardens were practically ruined.

In 1824 or 1825 there was an outbreak of fever in Jessore known as *jwar-vikar* which seems to have been very similar to the Burdwan epidemic of the eighteen-sixties in Bengal and the latter was almost certainly kala azar. Here an outbreak of fever occurred and in the course of three years devastated the division, causing, it is said, the deaths of no less than 750,000. The fever was believed to be malaria of a special type, designated by some 'typhomalaria,' characterized by relapses, progressive emaciation and enlargement of liver and spleen. It appeared to be com-

municable and to be imported by infected persons from infected places, spreading along lines of communication at the rate of about ten miles a year and showing a domiciliary and family incidence. In 1868 Dr French, the Civil Surgeon of Burdwan, reported on a 'contagious fever' with sequelæ in the following order of frequency enlargement of the spleen, diarrhœa becoming dysenteric, anasarca and congestion of the liver, in some patients he observed cancrum oris. He stated that it had appeared in the Jessore district in 1824 (v s), eight years later in the Nuddea district, in the Hooghly district in 1857, reaching Burdwan from both the last in 1862. It will be seen that, if these statements were correct, it had progressed slowly through some of the most populous districts of Bengal.

Two years before Dr French's report, Dr Wise, the Civil Surgeon of Dacca, observed that a contagious fever had been working havoc, practically decimating many villages of the division during the preceding four or five years. Nothing of this nature had been heard of prior to 1862 when an up-country boat arrived at Jageer on the Dulassery River, its crew dying from a low remittent fever, the disease had gradually spread thence. Jageer in 1862 was a large and prosperous bazaar, but in four years it had ceased to exist. Its people had been swept off by the fever, its houses had fallen in ruins and the site swallowed up in jungle. By the end of 1866 the disease had desolated several villages but had not succeeded in crossing the Mirzapur khal. The mortality was so great that in some years the dead were left in their houses or were thrown out into the jungle, bheel or river. The fever was ascribed by the natives to stoppage of the drainage of the country owing to a sandbank forming in the Dulassery River.

In view of the spread of the disease along lines of communication a few words on the history of the Brahmaputra Valley will be of interest. From the time of the end of the Mohammedan invasion in 1663 the Valley was undisturbed from India till the British occupation in 1826 and even then difficulty of communication proved a serious obstacle to development. In 1837 a journey from Calcutta to Assam took six to seven weeks. In 1834 trunk roads were opened on the north and south banks of the river and canal communication was set up with Bengal. Fourteen years later the first service of river-steamers was inaugurated on the Brahmaputra. The likelihood of introduction of kala azar was not great then, as journey by land was impossible through the tiger-infested jungle, unopened hitherto. In 1875 an outbreak of fever occurred among the Garos who gave it the name '*Sarkari*

Bemari ' or the ' British Government disease ' Seven years later it was still present and was regarded as a form of malaria of so severe a character as to be depopulating the Garo Hill districts of Assam and its gradual extension along the south bank of the Brahmaputra was observed

We hear little more during the ensuing seven years , then, in 1889, G M Giles was sent to Assam to investigate this disease and also the prevalence of hookworm and its effects He found ankylostome ova in most of the kala azar patients—Dobson showed that 80 per cent of imported coolies also harboured the worm—and concluded that " whatever kala azar might be elsewhere, the disease so-called in Gauhati [where he was working] was undoubtedly ankylostomiasis," and that " it is obviously absurd to attach any pathognomonic importance to the symptom [enlarged spleen] in connection with the etiology of kala azar," because splenomegaly, he said, was so common in healthy people He thus fell into one error by the same process as that by which he evaded another , had he reversed his statements—regarding the splenomegaly as a symptom of kala azar and the presence of hookworm ova as common in apparently healthy persons—he would have been more nearly correct

These dicta were not generally accepted and in 1896 Leonard Rogers, then a junior officer in the Indian Medical Service, was sent to Nowgong to investigate it afresh and, as he frankly admits, fell into a similar trap and concluded that kala azar was a spreading epidemic malaria, for 80 per cent of the patients in the district harboured malaria parasites He visited Sylhet where kala azar was then unknown, though malaria was common, and concluded that " the Assam disease was but an epidemic manifestation of the chronic malaria cachexia seen in Sylhet " Ross in 1899 came to the same conclusion Rogers, however, did good work in his investigations, in spite of arriving at an erroneous conclusion, for he described the clinical signs in detail and remarked the leucopenia , he showed also that the infection was domiciliary and that spread of it could be controlled by moving those affected to new sites In 1897 fevers were responsible, according to the returns, for 14,500 deaths in Nowgong, of which there is no doubt the majority were due to kala azar Less than a decade later, when more was known of the disease and its treatment, the deaths from kala azar (in 1905) were 379 only A survey carried out in 1912–13 showed that the endemicity had remained fairly stationary during the preceding four years The disease had almost disappeared from the higher levels of the Garo Hills, but at the foot,

on the south bank of the Brahmaputra, there was an endemic centre and villages farther up the Valley were infected. In Darrang district of Assam there was a fairly large endemic area, in Nowgong eighty-six villages were reported infected and the form of disease was more acute there. Clearly, certain endemic areas persisted 'as glowing embers in the old track of the epidemic fires,' and investigation showed that in these areas there might be a flaring up from time to time. Except at these points the disease was on the whole quiescent.

In 1901 Stephens and Christophers, in a Report to the Royal Society, 1902, stated that they had seen over eighty cases of "malarial cachexia and enlarged spleen," but were unable to find malaria parasites or pigmented leucocytes, or in fact any real evidence of malaria, and wondered whether the disease was "that somewhat dubious entity, kala azar." As long as six years afterwards Major B. H. Deare, Civil Surgeon of Patna, was writing regarding 'cachectic fever' or infection with Leishman-Donovan bodies, and said that "this form of chronic fever with enlargement of the spleen is common in the district, and up to a recent date was mistaken for malaria cachexia." The diffusion of knowledge of the differences between malaria and kala azar was a slow process.

In 1902, Bentley, on the strength of some serological tests carried out at Kasauli, declared the disease to be undulant fever.

Before we pass on to describe the causative organism and the developments which ensued in consequence of its discovery, we may fitly interpolate here a few further remarks on the epidemiology of the disease. A study of its outbreaks shows us that it is characterized by a slow spread, about ten miles in the year, and always along traffic routes, also that when it invades a village it seems to cling to particular houses and then spread from these to others, and thirdly that it does not diffuse itself generally over a district but settles in limited foci. Factors which appeared to influence epidemic spread were human cases of the disease, close association between the sick and the healthy, absence of any immunity, and certain conditions of soil and climate. Thus, Assam has a subtropical moist climate, with a maximum temperature of 90–100° F and a minimum of 40–50° F, and a humidity of 70–90 per cent, with abundant vegetation. The sporadic form which occurs in the Sylhet Valley of Assam, in Lower Bengal and Bihar, and in the eastern parts of the United Provinces is milder clinically and more chronic than that seen in epidemic outbreaks. In parts of Madras it occurs when humidity is high and the mean temperature is not below 50° F.

Further, kala azar seems to recrudesce after a succession of unhealthy seasons, as in the 'eighties and 'nineties, and more recently after the influenza pandemic of 1918-19. In India it appears to be essentially a cyclical disease, prevailing epidemically for a decade or so to be followed by a period of comparative quiescence for fifteen to twenty years, the site of an epidemic becoming an endemic focus. This has not received any satisfactory explanation, it may be that most of the susceptibles had been killed off (we speak of the days before the institution of antimony treatment) and a comparatively resistant population remained, till a new generation afforded fresh, susceptible nidus.

Yet another puzzling feature has been revealed by a study of past epidemics. Very soon after a fresh outbreak is noticed in a district, or even coincidently with it, we find all the smouldering fires which have been left from previous epidemics, in other and, it may be, often far-distant areas, burst out afresh and a widespread conflagration ensues involving the areas newly infected and those which had previously been the sites of outbreaks. This seems to contradict the general observation that extension follows lines of traffic.

In 1900 W. B. Leishman had observed at Netley certain bodies in the spleen of a soldier who had been invalided from Calcutta on account of 'Dum-dum fever'. He did not, however, place his observations on record until three years later (May 1903) in which year C. Donovan independently found the same 'bodies' in material from spleen puncture carried out on patients believed to be suffering from this form of 'malarial cachexia,' as designated by Rogers. These bodies have, therefore, been given the name of Leishman-Donovan bodies. Donovan announced his discovery in July, he was working in Madras and was examining blood taken from the spleen of a patient with this viscus much enlarged, who exhibited emaciation, irregular fever and diarrhoea. Wright in December of the same year found them in the lesions of 'tropical ulcer'.

The following year Rogers cultivated this protozoon and showed that under certain circumstances a flagellated form appeared. He found that by mixing splenic blood with sodium citrate to prevent coagulation and keeping the mixture at 22°C, the parasite multiplies and later assumes a form resembling a trypanosome but without an undulating membrane. He suggested that the bed bug, *Cimex lectularius*, might be the transmitting agent (v 1).

The Leishman-Donovan bodies aroused much interest and were studied by several workers, notably Christophers, Ross, Laveran, Mesnil, Manson and Low. The best description is that by the first-named in 1904, in *Memoirs by Officers of the Medical and Sanitary Departments of the Government of India*. In 1904 Marchand and Ledingham described (in the *Lancet*) certain bodies seen by them two years before in sections of spleen, liver and bone-marrow of a patient who had suffered from irregular fever and enlarged spleen.

2 TRANSMISSION

As stated above Rogers, in 1904, had suggested that the transmitting agent was an insect vector, probably *C. lectularius*. The bug was suspected for some years though convincing evidence was not forthcoming. Many of the reasons adduced were epidemiological, such as that the disease tended to a domiciliary limitation and to prevail more in insanitary localities, these conditions might, however, be purely coincidental and the same arguments would apply to lice and fleas, and even flies. The only scientific grounds were that experimentally developmental stages of the parasite could be observed to take place in the bug.

Donovan did not share this opinion and stated, as early as 1909, his dissatisfaction with the evidence, as regards *C. rotundatus* at least. He suggested *Conorrhinus rubrofasciatus*, known in Madras as the 'mother of bugs'. This was supposed to suck human blood and also to feed on the common bed bug [if so the local name would appear to be a misnomer]. This insect is widespread both within and outside India and is nocturnal in its habits. The reasoning is no more cogent than that in favour of the bug itself. Although in 1918 experiment showed that the flagellate stage could survive in bugs to the twenty-ninth day, attempts at cultivation of the flagellates from the rectum of the insect were unsuccessful and the conclusion was drawn that infection by the faeces was highly improbable.

In spite of much research the mode of infection remained undecided. At the Indian Science Congress held in 1922 a discussion took place at which Patton expressed the opinion that the 'bed bug theory' was nearly complete. He excluded mosquitoes, fleas, lice and ticks on various epidemiological and experimental grounds, and did not think sandflies could be the vectors, at all events in Madras. *Conorrhinus* he also ruled out because, though it might occasionally bite man, it did not usually feed on him. As regards sandflies, he failed to infect 384 sandflies

which had been allowed to feed on kala azar patients although 10 per cent were found naturally infected with *Herpetomonas*. As regards *Cimex hemiptera* Patton recorded successful experiments with it and also noted that it was common in Madras.

Basile, working in Sicily in 1912, had incriminated fleas as transmitting the form of kala azar which was found along the Mediterranean littoral. This form appeared to attack children chiefly and was, therefore, designated infant kala azar. It had been described clinically in Italy in 1880. Except for its greater incidence in the young it differed in no obvious character from the eastern form. Basile found that fleas, after feeding on spleen pulp containing the parasites, were able to infect dogs, and also that healthy dogs became infected if they were confined in the same cage and fleas were present, further, that dogs could be infected by fleas brought from a distance from a house in which dwelt kala azar patients. *Pulex irritans* and *P. serraticeps* were both capable of transmitting infection and, the parasites being present in the faeces of the insect, he maintained that indirect transmission was also possible.

On account of the peculiar distribution of kala azar in India Sinton in 1922 suggested the sandfly, *Phlebotomus*, as an insect vector and the same year L. E. Napier found that the topographical distribution of kala azar cases and *Phlebotomus argentipes* closely correspond. F. P. Mackie was probably the first to note this association. "The only insect which has given any return for the work put into it is the sandfly, and I am of opinion that the relation of this insect to the disease would repay further investigation." Eleven years prior to Sinton, in 1911, C. M. Wenyon had put forward the suggestion that *Phlebotomus* was the transmitter of the parasite of Oriental Sore, the brothers Sergent proved the correctness of this in Africa later.

A big advance in determining the vector and the mode of transmission was made in 1925 by the team-work of members of the staff of the Calcutta School of Tropical Medicine, namely R. B. Lloyd, R. Knowles, L. E. Napier and R. O. Smith, work subsequently confirmed by S. R. Christophers, H. E. Shortt and P. J. Barraud of the Indian Kala Azar Commission. Napier by epidemiological studies, Lloyd by serological tests, and all four by experimental entomological research, found that in the crowded northern Indian part of the city most of the cases were imported and that from them only a few infections were promulgated, in the south with mixed races and many Anglo-Indians nearly all were locally infected. Moreover, in the former, there was little

vegetation, the houses had paved courtyards, the cattle were kept below and human beings slept in the upper storeys. In the southern areas there was vegetation close to the dwellings and people slept on the ground floor. They observed that masonry buildings provided relatively more cases than did bamboo huts. Lice and bugs were equally common in north and south, sandflies and *Culicoides* were particularly prevalent on ground floors. Incidence of kala azar was highest among persons living in one-storeyed buildings in the suburbs.

By precipitin tests they found that *P. argentipes* in the northern areas fed on cattle rather than on man, in the southern more on human blood. This may be expressed in another way, where cattle were stalled on the ground floors and human beings lived above the insect fed on the former, but when human beings slept on the ground floor they were bitten by the sandflies. Thus the greater prevalence in the southern area would be accounted for, if *P. argentipes* is the vector.

Approaching the problem from another angle they showed that after *P. argentipes* has been permitted to feed on kala azar patients ten out of eleven bred in the laboratory, and therefore clean, were found on the third to fifth day afterwards to have leptomonad forms in the fore- or mid-gut and in some the infection was heavy although blood films of the patient contained but few Leishman-Donovan bodies. By the twelfth day there was massive infection of the whole pharynx and free-swimming forms were observed, by Knowles, Napier and Smith, to extend to the front of the buccal cavity close to the biting mouth parts. In July 1926, they found a fly naturally infected in a house in which was a kala azar patient, but even by 1930 no proof had been obtained of the natural mode of infection of man, for neither animals nor man had been observed to acquire it through the bite of infected sandflies.

The Kala Azar Commission of India in their First Report, 1926, confirmed this work and found that the infection of the insect was so heavy in some instances that at its next feed inoculation would be inevitable. The report adds "Only experimental transmission by the sandfly would therefore now seem to be necessary to prove finally the rôle of this insect in the transmission of kala azar."

W S Patton and E Hindle later, in 1927, demonstrated that a similar development took place in the sandfly of China, *P. sergenti* and in *P. major* var. *chinensis*, and that the flagellates grow forward and extend to the tip of the proboscis and, though

these flagellates produced infection when inoculated into hamsters, bites by the insect did not convey it. The range of flight of this insect is limited, hence, as we shall see later, removal of inhabitants from a village obviates infection and prevents spread. Patton and Hindle found the hamster, *Cricetulus griseus*, a convenient animal for experiment. (It had originally been made use of in 1919 by Dr E T Hsieh at the clinical laboratory, Peking Union Medical College, as a substitute for the white mouse in grouping pneumococci.) They found that this animal's skin becomes heavily infected without production of symptoms or of visible lesions. In 1929 Shortt, Barraud and Craighead were able to infect eight out of ten hamsters by oral administration of cultures of *L. donovani* and also by feeding them with infected organs. Whether the natural mode of infection, therefore, was oral or by injection was left undecided, for attempts experimentally to infect the hamster by bites of sandflies were not successful¹.

Here is a fit and convenient place to sum up the findings as given in the two Reports of the Indian Kala Azar Commission, of S R Christophers, H E Shortt, P J Barraud and L E Napier. The chief conclusions of the First Report were

1 That the distribution of kala azar in India is associated with the existence of alluvium and a certain heaviness of rainfall

2 That, if the sandfly is the vector, *P. argentipes* may be the species carrying infection in India, but, to account for the presence of kala azar in other countries, more than one species must be able to transmit it

3 That the fact of young children being frequently infected, children who never go beyond the precincts of their houses, is opposed to the view that a jungle-inhabiting blood-sucking insect is the vector

4 That there is very definite evidence of house infection, in many cases traceable to the introduction of a relative or other person from a house known to be previously infected

5 In Assam the conditions include a high degree of humidity, a still air and a uniformly moderate temperature, in Madras, conditions are very different, the houses are not lightly built but are masonry habitations densely packed, and there *P. argentipes* abounds

During the next two or three years the Commission was occupied in transmission experiments with *Phlebotomus* and investigations as to the mode of conveyance of the parasite by the bite of this fly, in search for naturally infected *Phlebotomus*,

¹ Lately, a small number of successful transmissions of kala azar by the bite of the sandfly have been effected in India

in testing the infectivity of the forms of the parasite seen in infected flies, and the infectivity of the flagellated forms in culture, the life-history of the parasite in the fly, and in the diagnosis and treatment of kala azar

Previous work had demonstrated that infected *Phlebotomus* carried the parasites in their buccal cavities and the conclusion was drawn that, when sucking blood, the fly transferred them into the wound. This was not confirmed in spite of many experiments on the Chinese hamster, on white mice, and even on human volunteers. It was understood, of course, that the incubation period might be a long one.

In 1930 the Commission brought its investigations to an end because the epidemic had declined and the character of the cases was changing from the acute fulminant type which prevails under epidemic conditions to the more chronic 'inter-epidemic' type, which was not suitable for experimental work. Their report reviews the position relative to transmission by the bite of the sandfly. They regard this as the most attractive hypothesis, but evidentially oral transmission had strong support, or a combination of the two, ingestion of the products of crushing the flies. Possibly some accessory or predisposing factor was thought to be needed, thus, the 1890-1900 outbreak was preceded by a devastating earthquake, that of 1917-29 by the influenza pandemic. There was no evidence at all in favour of infection being conveyed by hookworm larvae.

Southwell and Kirshner have studied the question of transmission during the past year (1938) and have come to the following conclusions (*Ann Trop Med and Parasit*, 1938, Vol 32, pp 95-102)

- 1 It is not yet proved that infection results by inoculation of leptomonads from the bite of an infected *Phlebotomus*

- 2 In the sandfly both leptomonad and leishmanoid forms occur in the mid-gut and similar forms occur in cultures

- 3 The positive results obtained by inoculation of infected sandflies, and also by cultures, into man and animals may possibly be explained by the presence of these leishmanoid bodies both in the insects and in the cultures

- 4 It is possible that transmission of leishmaniasis occurs as the result of infected sandflies being crushed on the skin, and that the infective stage is the leishmanoid body

- 5 Sufficient attention has not been directed towards infected nasal discharges as a method of transmission of kala azar

In connection with these conclusions, especially the third, it

is to be noted that the suggestion that it is only the leishmania forms and never the flagellate stages which infect is not in accord with present knowledge and belief

When discussing the question of the flea as a possible vector (p 554 above) we mentioned incidentally the form of kala azar which is met with along the Mediterranean coast This demands more detailed notice and we must retrace our steps

Very soon after the discovery of Leishman and Donovan was made known, in fact in the following year, 1904, the Mediterranean form was recognized Cathoire observed in films from the spleen of a child in Tunis bodies which Laveran recognized as Leishman bodies Pianese saw them in 1905 and two years later, in 1907, Nicolle and Cassato found them in the spleen of another child Further investigation showed that 'infantile kala azar' existed in Crete (recorded by Archer), in Sicily (Gabbì), Malta (Critien), Spezzia (Gabbì), and Paras (Christomonas), under various local names It was found to be endemic also in Algeria, Tunis, Tripoli, Libya, Egypt, the Sudan—Pirie who had been working in the Sudan died in England from kala azar in 1907—Asia Minor, Greece, the Ionian Islands, Italy, the southern and eastern coasts of Spain and the west coast of Portugal

Further study showed that along the Mediterranean littoral dogs also were naturally infected In 1909 Donovan noticed the presence of Leishmania in dogs in Tunis, where infantile kala azar exists He examined 1150 dogs in Madras, but without finding any infected, in 1910 Bousfield, studying kala azar in the Sudan, collected forty-two cases, fifteen on the Blue Nile, and in the spleen of a dog belonging to a patient suffering from acute kala azar Leishmania were found

Because of the presence of the disease in dogs and also because there was some difference in the symptomatology, the Mediterranean form, the so-called infantile kala azar, was thought to be distinct from the Indian In Malta, according to Adler and Theodore, 10 per cent of native dogs are infected These authors believe that here and in Catania, Sicily, both human and canine parasites are transmitted by another species of *Phlebotomus*, *P perniciosus* As a result of inoculation experiments Adler has come to the conclusion that Leishmanias of man and dogs are not clearly defined species but are to be regarded as strains undergoing evolution and under differing circumstances, for there is no simple character by which one so-called single species can be constantly differentiated from another The question is important, for if canine kala azar is caused by the same parasite as that

producing the human disease, the dog may be a reservoir of the human virus

In Greece, according to Bensus writing in 1931, human kala azar is most prevalent where dogs are kept and these animals are often attacked by the disease. On these dogs ticks are common, *Rhipicephalus sanguineus*, the parasite can live in the tick, animals can be infected by inoculating them with infected ticks, and some authors believe that the tick may be a vector of kala azar.

This question of the identity or otherwise of *Leishmania donovani*, *L. canis* and *L. tropica* was intensively studied in 1928 by N. J. Chodukine and M. S. Soffieff by serological tests with strains of *Leishmania* on mice, guinea-pigs and rabbits. By the adhesion phenomenon with cultures of *L. tropica*, *L. donovani*, *L. canis* and the cutaneous form of the last no differences were detectable. When immune serum was added to cultures, it was found that *L. donovani* antiserum lysed its homologous organism and both forms of *L. canis* but not *L. tropica*, and that *L. tropica* antiserum was specific in its action. The same results were obtained by agglutination and absorption tests. From these it would appear that *L. donovani* and *L. canis* are identical, but that *L. tropica* is distinct. Whether the two forms of *L. canis* were identical or merely related was not decided from their experiments.

From a large number (4000) post-mortem examinations of dogs, however, Chodukine and Soffieff concluded that cutaneous canine leishmaniasis was merely a symptom of a generalized infection, in some with prominent skin lesions parasites were present also in the spleen or bone marrow, while in a considerable number of apparently healthy dogs leishmania were found in the hair follicles and sebaceous glands. In short, these cutaneous lesions in dogs were regarded as analogous with those of hamsters inoculated with *L. donovani*, and with Brahmachari's 'dermal leishmanoid' in kala azar in India.

There are certain peculiarities worthy of note. Thus, canine infection is most intense in the summer, in children along the Mediterranean mostly at the end of winter and the beginning of spring. Indian kala azar, even in regions heavily infected, is rarely seen in dogs, and in Bengal no connection could be traced between human and canine cases. Even in areas where infantile kala azar is common dogs often showed no infection though kept in houses where was a human patient, yet inoculation of the human parasite into dogs produces disease indistinguishable from the natural canine affection. The situation is summed up

by Wenyon in the following words which state the problem clearly

Though it is admitted that the human and canine diseases are caused by the same organism, this does not mean that the dog is to be regarded as a reservoir of the virus. Some have maintained that in Italy the disease necessarily passes from dog to man, but so many cases occur which cannot be associated with any infected dog that it would appear that the infection of the animal is as much an accident as the infection of the human being. Areas occur in which apparently only dogs have the disease, while in others only human cases are known (*Protozoology*, p 413)

3 DIAGNOSIS

One aspect of the question of diagnosis has been dealt with above (pp 550-1) when we pointed out the confusion between kala azar, ankylostomiasis, malaria and undulant fever. The methods of diagnosis, however, of this disease have some historic interest, especially laboratory diagnosis.

The earliest laboratory test was the finding of the parasites by direct examination of the peripheral blood, this had been mentioned by Christophers, Donovan, Patton and others. Next, after Rogers had cultivated the protozoon in 1904, came this method, using N N N medium and fluid from the spleen or liver or the peripheral blood, at the same time direct examination of smears of spleen or liver pulp might reveal the parasites. In 1913 (see above) Cochrane remarked on the value of examining smears from the cut surface of excised lymph glands, and these methods, apart from clinical diagnosis, were utilized until Brahmachari in 1917 published his 'globulin precipitation test,' based on the fact that more globulin was present in the serum in this condition than in any other known. For performing this, some serum from the patient was added to twice that quantity of distilled water, in positive cases a precipitate formed. Next came Napier's 'formol gel test,' described by him in 1921. It was a test adapted from that which had been suggested for the diagnosis of syphilis. In the case of the latter, it was found that the serum of a syphilitic subject became 'jellified' in 24-30 hours when two drops of commercial formalin (40 per cent formic aldehyde) were added to 1 c.c. of the patient's serum. In kala azar a similar admixture gave rise to immediate opacity and jellification in half an hour. The test was not given by malaria patients nor in cured cases of kala azar. Fox and Mackie discovered the same test independently the same year.

In 1927 R. N. Chopra, J. C. Gupta and J. C. David published

an account of their test of adding some pentavalent antimony preparation to the serum, the result being the formation of a precipitate. The findings ran parallel with those of Napier's reaction. In the same year a corpuscle sedimentation test was proposed by E C Hodgson, A C Vardon and Z Singh for differentiation of kala azar from malaria, enteric, tuberculosis and other fevers, the diagnosis being made on the rate of sedimentation and the characters of the supernatant fluid. After employing the antimony and the aldehyde tests in parallel investigators came to the conclusion that more positives were given by the former and it had the further advantages that less serum was required, that the result was forthcoming immediately and was given earlier in the disease. A simplified form of the test was evolved by which one or two drops of blood were added to 0.25 c.c. of 2 per cent potassium oxalate solution, to a little of this mixture in a Dreyer's tube was added a 4 per cent solution of a urea-antimony salt (urea-stibamine), the fluid being passed down the side of the tube by means of a capillary pipette so as to underlie the oxalated blood. In a positive case a flocculent precipitate formed immediately at the junction of the two fluids. The explanation adduced is that there is an excess of euglobulin in the blood in kala azar and decrease in the serum albumen, and the globulin albumen ratio rises from 0.66 to over 2.9. (It falls rapidly again under successful antimony treatment and is, therefore, of value also as a gauge of the latter.) Tested in 256 kala azar patients a positive result was obtained in 235 as compared with 184 with the aldehyde test. In very early cases the flocculence may not appear for 10-15 minutes.

In 1930 L E Napier and C R Das Gupta proposed another diagnostic method, namely intravenous injection of an ordinary therapeutic dose of urea stibamine (0.2 gm. in 4 c.c. distilled water). This causes an increase in the number of Leishmania in the blood of a kala azar patient, greatest 5-10 minutes after the injection. For example, a patient showing, say, ten parasitized cells before injection showed thirty-four ten minutes after. The authors regarded this as a valuable diagnostic procedure in cases in which puncture of spleen or hæmoculture was not feasible.

4 TREATMENT

The fact that removal from an infected district was a preventive measure was known early in the history of this disease, but wide application of such means was an expensive undertaking. Moreover, it did not always succeed, for in spite of migration of

the unattacked and prevention of movement of the victims and limitation of communication between infected and healthy villages gradual diffusion might take place and year after year a fresh batch of cases might be discovered in villages till then free

At times, however, such measures would prove highly satisfactory Dodds, Price and Rogers in 1914 had great success in eradicating the disease from tea-gardens by segregation in a dangerous focus in Gholaghat which was becoming a menace to districts hitherto uninfected A house-to-house survey was carried out, families found infected were removed to new lines 300-1200 yards from their old site, the houses evacuated and they, together with the bedding and clothing of the inhabitants, being burned, compensation being given At the end of three years they reported only one more case of infection among forty removed families Control lines left in their original condition of course remained infected and coolies newly introduced into them were attacked-

In older times it was most disheartening to visit the infected villages and, erroneously regarding the enlarged spleens as malarial, to dispense quinine to the inhabitants The discovery of the curative effects of antimony—tartar emetic—by injection changed the entire outlook and converted a 90 per cent fatality rate into a 90 per cent recovery rate Since 1920 whenever kala azar cases in any number have been discovered a qualified man has been appointed to look after them, and in four successive years the number treated has increased till the last is five times the first, the figures being 7188, 15,888, 19,659, and 37,300 The reception of treatment was made compulsory Since this treatment has been introduced there has been no further explosive outbreak

Early treatment is not merely curative but preventive, for a threatened outbreak can be controlled thereby, as in a tea-garden for example New cases are carefully looked for among the coolies, for if infection should go unrecognized and obtain a footing a 'site infection' is set up and it would seem that under such circumstances no amount of treatment is able to prevent a constant crop of cases, and if these become numerous there is only one remedy—evacuation of the lines and establishment of new ones at a distance

The favourable effects of intravenous administration of tartar emetic were noted by Leonard Rogers (*British Medical Journal* and *Indian Medical Gazette*, 1915) and by G di Cristina and G.

Caronia (*Journal of Tropical Medicine*, 1915) independently They used a 2 per cent solution, the initial dose being 4 c c, increased gradually to 10 c c This drug had been recommended two years earlier, in 1913, by Gaspar Vianna for the South American cutaneous leishmaniasis In 1918 Rogers suggested sodium antimony tartrate as being a little less toxic than tartar emetic, certain fatalities having been reported from use of the latter The following year he proposed another substitute, colloidal antimony sulphide, 1 in 500 solution being used after being made isotonic with 5 per cent glucose, and 0.5 per cent phenol added as a preservative Good results were reported from its employment and it is much less toxic than either the sodium or potassium antimony tartrate

In 1929 L. E. Napier reported good results from the use of pentavalent compounds of antimony With aminostiburea, which is well tolerated in comparatively large doses, he found that an average total dosage of 2.3 gm would bring about a cure in more than 90 per cent Neostibosan, diethylamine-*p*-aminophenyl stibinate, or, shortly, 693B, is another antimony compound with low toxicity but high curative value Five per cent solution usually suffices, but five times this strength can be given, in a dose of 0.2 gm It proved equally efficacious intramuscularly, 0.3 gm in 25 per cent solution being isotonic with the tissues and almost painless When administered intravenously injections are given on eight consecutive days

A new drug, solustibosan, has recently (1938) been introduced which is reported as superior to neostibosan Solustibosan, or 561, is a sterile isotonic neutral solution in water of a pentavalent antimony component One c c of this solution contains 20 mgm of antimony

Yet one more preparation deserves mention, Burroughs Wellcome's Neostam or stibamine glucoside It and urea stibamine are of great value in kala azar, having a relatively low toxicity and being well tolerated by man in comparatively large doses

II ORIENTAL SORE CUTANEOUS LEISHMANIASIS

1 EARLY KNOWLEDGE PREVALENCE

Oriental Sore has several synonyms, many of them place names, such as Delhi Boil, Aleppo Boil, Bouton de Biskra, Bouton de Baghdad, Sart Sore, Pendeh Sore

The usually accepted history of the discovery of the parasite

of Oriental Sore has to be revised as the result of the studies of Dr C A Hoare who has done good service to tropical parasitology in translating the original account of Borovsky which appeared in a Russian journal, *Voenno-Medicinskiy Zhurnal*, in November 1898, a journal difficult of access, and in a language with which very few tropical workers are acquainted (Dr Hoare's translation appears in the *Trans Roy Soc Trop Med and Hyg*, 1938, v xxxii, No 1, pp 78-90)

Though long known clinically it was not until 1885 that the associated parasite first received mention when D D Cunningham saw and described some deeply staining bodies which he observed in "certain cells larger than lymphocytes" He thought that the former were causative parasites, 'sporoid bodies' or 'nucleoid bodies,' in a large plasmodial cell, the whole *Plasmodiophora* Six years later, in 1891, R H Firth confirmed the presence of these 'intracellular structures' and refers to what had been called *sporozoa furunculosa*, not, however, giving them a generic and specific name but intending to imply "spore-like bodies found in association with boils" In Firth's opinion, however, these were not parasites but degenerative changes in the cells

In the meantime Borovsky, who in 1892 had been appointed to the charge of the Surgical Department and the Bacteriological Laboratory at the Military Hospital, Tashkent, had been studying Sart Sore, its aetiology, pathology and treatment, and in 1898 published his results in the article referred to above He found organisms, *Staphylococcus aureus* and Streptococci, as others had before him—Duclaux, Heidenreich, Chantemesse, Nicolle, Rapt-schewsky—but Borovsky did not, as they had done, regard them as causative, his attention was given to "small spherical, oval or fungiform corpuscles," 1.5-2.0 microns in diameter, with a nucleus and a "process running from it to the periphery" He, as distinguished from Cunningham, regarded these as protozoa and the cause of the disease

Perusal of Dr Hoare's translation convinces one that Borovsky was the first to describe the protozoon later known as *Leishmania tropica* His colleague, K Shulgin, confirmed, in cases of Pender Sore, the findings of Borovsky in Sart Sore

Twelve years after Firth's paper appeared, J H Wright described in smears from an Oriental Sore in a child from Armenia round or oval bodies, 2-4 microns in diameter, massed in endothelial cells He named them *Helcosoma tropicum*, and Marzinowsky and Bogroff the following year found them in a boy who came from Persia, they gave these bodies the name *Ovoplasma*

orientale When later investigation showed that the parasite belonged to the same genus as that causing kala azar, *Leishmania*, Wright's specific name held good and the parasite became *L tropica*, though it is not distinguishable, morphologically, or culturally, from *L donovani*

The accepted views regarding Oriental Sore towards the end of last century may be seen from a statement in the Report on Sanitary Measures for India, 1875-6, where we find that Oriental Sore or Delhi Sore is "an instance of the dependence of a local malady on the nature of the water supply," and it occurs "when the water is very hard and contains a large quantity of salts" It was known that Delhi sore was merely the local name for a condition met with in other parts of the world, but in Delhi it was seen also in dogs, was considered to be contagious and reproducible by inoculation Prevention was summed up in general and personal cleanliness, the use of pure or boiled water for drinking, attention to the sanitary state of the locality, avoidance of overcrowding and contact with the disease either in man or animals, particularly dogs The disease, it was held, was contracted by bathing or even washing in the foul water of Delhi, which was 'comparable with sewage,' the infection gaining entrance by small wounds, sores, bites, scratches

Sir Risdon Bennett (*Diseases of the Bible*) states that in Delhi a disease characterized by boils has been prevalent from time immemorial, and used to be called *Aurungzebe* after the Prince who reigned there in the eighteenth century, he is said to have died of the disease

When Wright, in 1903, established the parasitic nature of the bodies described Manson suggested an analogy between variola and vaccinia on the one side and kala azar and oriental sore on the other, based on the view that one attack of the latter confers immunity from future attacks, and that in India, where kala azar is common (see later for distribution) oriental sore is not and *vice versa* Further, kala azar had a high fatality rate, oriental sore was more benign Following up his analogy, Manson also suggested that inoculation should be performed with cultures of *L tropica* as a prophylactic against subsequent infection by kala azar Nicolle claimed to have succeeded in producing some degree of immunity to generalized leishmaniasis in dogs and monkeys by intraperitoneal injection of cultures of *L tropica*

D B Thomson and A Balfour in 1910 described a non-ulcerating nodular form of Oriental Sore in Egyptian soldiers These small nodules, each the size of a pea, occurred in groups with secondary

nodules at the periphery which later joined up with the central mass. They showed no signs of breaking down, they contained *Leishmania* and were most frequently seen on the face, shoulders, arms and thighs. These were noted also by C M Wenyon describing his work on *Leishmaniasis* in Baghdad. He found that nearly all the inhabitants suffered at one time or another, mostly in childhood, and that one attack usually proved protective for life. Owing to the fact that more cases occurred in the autumn at the time of ripening of the date, another synonym was Date Boil, which on healing left 'date scars'. Wenyon observed two clinical types. The ordinary ulcerating form which often became very foul owing to secondary contamination, and the raised, nodular, boil-like form with unbroken surface, the parasites being seen in the puncture fluid. The condition usually persisted for a year or so and in those days no treatment seemed to be of any avail. Various insects were suspected as carriers and slight development was observed in the house-fly and in bed bugs. Mechanical conveyance by the former was thought to be highly probable. *Aedes* was also prevalent in the district and herpetomonad forms were observed in the mid-gut after a feed on one of these sores, but there was no satisfactory evidence of its capabilities as vector.

In the course of the ensuing decade the distribution of cutaneous leishmaniasis was found to be much more widespread. In certain countries its area of prevalence was sharply marked off from that of kala azar. Thus, in India oriental sore was met with north-west of a line joining Bombay and Delhi, whereas kala azar occurred only to the east of this line, in Northern Africa oriental sore was found at Gafsa, kala azar around Tunis, two degrees farther north. In other places—Turkestan, the Mediterranean littoral, the Blue Nile district of the Sudan, for example—both kala azar and oriental sore were seen. According to Gerschenowitsch they are found side by side in Central Asia, perhaps in a single family, and, very rarely, both in the one patient. It is stated that recovery from a cutaneous infection does not necessarily protect against subsequent infection by the same type [this is contrary to general experience] nor against infection with kala azar [as Manson hoped from his suggestion (see p 565 above)]. It was stated further that concurrent infection with both did not affect the course of either.

Apart from its well-known occurrence in India, Arabia, Persia, Mesopotamia, the Caspian and along the Mediterranean, its presence had been recorded in the Niger district by Stévenel and Benoit-

Gonin in 1911, in Abyssinia by Martoglio in 1912, in Dahomey and Nigeria by Wagon in 1914, in the French Congo by Bouilliez in 1917

Meanwhile there were many records of its presence in the New World, a few may be mentioned here. The leishmanial cause of the ulcer of Bauru, Brazil, had been noted by Lindenberg, Carini and Paranhos in 1909, and the association of naso-pharyngeal ulceration, 'espundia,' was observed by Carini in 1911. Two years before Nattan-Larrier had seen cases of oriental sore in the Guianas, where it went by the names of Forest Yaws, Bosth Yaws, Pian Bois—all indicative of a resemblance to, or possible confusion with, yaws—and had observed that in some cases there was involvement of the nasal mucosa. Seidelin recorded its existence in Yucatán in 1912, Strong in Peru in 1913, Migone in Paraguay the same year, Iturbe noted it in Venezuela in 1917, and Escomel saw it the same year in Bolivia. In 1918 Inchaustegui observed it in Mexico among gatherers of chicle gum, in some districts half the workers were attacked, the lesions being particularly common on the ears, in 1920 Tejera reported it in Colombia, but here the nasal infection was rare. Generally speaking, the American form differed from that of the East in being more chronic in its course, in, at times, involving the lymphatic system, and in setting up ulceration of the nasal and pharyngeal mucosa.

This last—*espundia*—was seen in various parts of South America—Brazil, Bolivia, Peru, Guana, Uruguay, Paraguay (where it has at times become epidemic) and less frequent in Colombia, Venezuela, Ecuador, the Argentine—and also in Yucatán, Panama, Martinique and rarely in other West Indian islands. There are indications that the condition is of old standing in South America, for engraved figures on ancient Inca pottery depict facial mutilations closely resembling those of *espundia*. Cases have been reported from the Sudan, Somaliland and even Italy, but these may have been instances of invasion of the mucosa from adjacent cutaneous lesions.

There is little doubt that the disease is increasing in prevalence in Brazil. Thus in 1914 at a certain hospital for venereal and skin diseases 13 per cent of the patients were treated for *espundia*, in 1919 the proportion was 48 per cent. Also in the five years 1914–19 at São Paulo, of 15,000 persons treated for dermal leishmaniasis 20 per cent were suffering with *espundia*.

2 TRANSMISSION

As regards transmission we have mentioned above the suspicions which were attached to the house-fly, the bed-bug and

Aëdes Laveran stated, speaking of the Bouton de Biskra, that in September and October the slightest wound tended to become transformed into the 'bouton' and that flies carry the virus on their feet and proboscides and so give rise (mechanically) to infection

To Shulgin, however, belongs the honour of suggesting that the disease, the infection at least, is transmitted by some blood-sucking insect This he did in a paper on Pendeh Sore in 1902 In this he says [we quote Dr Hoare's translation]

I am inclined to consider that the mode of penetration of the infective agent into the body is the same as that recognized at present for marsh fever, *i.e.* that it has an intermediate host—a mosquito or some other nocturnal biting insect,

and he supports this by the observation that in a certain part of Turkestan officers and men occupied the same barracks, but the former slept under mosquito nets and only the men were attacked

Wenyon, in Baghdad, in 1911 suggested the sandfly as a vector, a suggestion which Pressat had made in 1905 Wenyon found 6 per cent of *Phlebotomus* in Aleppo harbouring leptomonas, this was confirmed eight years later for *P. minimus* in India by Mackie, and for *P. minimus* and *P. papatasi* in Mesopotamia and Palestine by Patton In 1915 the brothers Sergeant, together with Lemaire and Sévenet, tried by means of *P. minimus* to infect man, monkeys and mice, but ineffectually The first-named had tried ten years before to produce the infection by the bite of a sandfly in Biskra (Wenyon) In 1921, ninety-four of these insects, *P. papatasi*, were collected at the Military Hospital, Biskra, and sent to the Sergeants at Algiers, where oriental sore was not known to occur Of the total seven arrived alive, these were broken up and applied to the scarified arm of a man who, two months and twenty-four days later, developed an oriental sore, proving the *P. papatasi* can harbour the virus at least for the three days occupied in transit from Biskra to Algiers

In 1928 S Adler and O Theodore brought forward evidence of cyclical transmission of *Leishmania* by sandflies, kala azar by *P. argentipes*, *L. tropica* by *P. papatasi* They found that the flagellates did not pass beyond the mid-gut but, avoiding the hind-gut, migrated to the œsophagus, œsophageal diverticulum and pharynx, the long forms predominating after the fourth day They were of opinion that this was the infective form Inoculation of these œsophageal forms into a volunteer produced a papule in five weeks Repetition of the experiment gave incubation periods ranging up to 120 days They also showed that Leish-

mania from the experimental sores (*Leishmania* obtained from naturally infected sandflies) were serologically identical with, at all events were indistinguishable from, those of oriental sores occurring naturally in Palestine and Baghdad Adler and Theodore had shown that the flagellates were located in the mouth parts of the flies, but the missing link in the chain—proof of infection by bites of the sandflies—is still to be found

The following year E A Mills, Chief Pathologist to the Government of Iraq, C Machattie, Veterinary Research Officer, and Major C R Chadwick, Director of the Civil Veterinary Department, Iraq, studied experimentally and epidemiologically the relationship of human and canine dermal leishmaniasis *P sergenti* and *P papatasi* have been shown to be the probable vectors of *L tropica* in man and they can also be infected with cultures from canine lesions and they feed readily on the dog It was found, moreover, that in Iraq at least, human and canine dermal leishmaniasis have a similar seasonal incidence, in both there are definite urban areas with a high and a low infection rate and in the latter there appeared to be a definite association between the two types, in both, infection occurs in unprotected parts—in dogs the internal surfaces of the ears, the nose, and margins of the eyelids—the serological reactions indicate very close relationship, if not actual identity and, as stated, there was strong evidence that the insect vectors were the same

The presence of *Leishmania* in ulcerative lesions in dogs was no new discovery, it had been noted by Neligan in Teheran in 1913, and found by Et Sergeant and his co-workers in Algerian dogs in 1924 and the same year by Mangin in Aleppo

In South American dermal leishmaniasis *Tabanidæ*, *Simulidæ*, and *Chironomidæ* have all been incriminated, but no proof of their acting as transmitters has been furnished and the later and more probable suggestion is a *Phlebotomus*, *P lutzii* In 1920 Cerqueira reported the development of ulcers at the sites of punctures by this Brazilian species of sandfly The experiments carried out by Aragão in 1922 were not altogether satisfactory—he worked on lines similar to those of the Sergeant brothers in Algiers, using *P intermedius*—because, as Wenyon has pointed out, the transmission might have been merely mechanical, not cyclical

CHAPTER X

LEPROSY

1 GENERAL AND INTRODUCTORY

Available historical records are not sufficient to enable us to decide where leprosy originated. Those who have most studied the question incline to the view that its first home was Africa, a country where to-day the endemicity is greatest. The belt of land extending across central Africa from Nigeria to Abyssinia is still the most severely affected in the world and it is thought that this was the primary home of the disease. But even in prehistoric times it had already spread to India and Egypt, for in the former reference is made to it in the Vedas, of 1400 B C, and even prior to this the Ebers' papyrus, a century and a half earlier (1550 B C), speaks of 'Uchedu' and 'Chon's swellings' and the description closely resembles that of leprosy. Two hundred years later, in 1350 B C, there are records in the reign of Rameses II which seem to point to the disease being present among negro slaves brought from the Sudan. Hirsch, giving as his authority Brugsch's *Histoire d'Egypte*, states that the disease is mentioned as prevailing in Egypt in 2400 B C in the reign of Husapti.

It is certain that leprosy has been common for 3000 years in Africa and India and Egypt and that it has spread eastwards from India and round the eastern Mediterranean from Egypt. It does not seem to be mentioned in Chinese medical works prior to 200 B C, though according to Schmid (*New York Med Rec*, 1869) it was present in Japan in the thirteenth century before Christ.

In Jewish writings and in the Bible occurs the term 'zaraath' which probably included not only leprosy but other diseases, in particular psoriasis and leucoderma. Gehazi who went out from the presence of Elisha "a leper as white as snow" was most probably infected with psoriasis from Naaman's gift of raiment and Naaman was cured by the agency of the sulphurous waters of the Jordan—the waters of the Jordan valley were found to be sulphurous by troops engaged in the Palestine campaign in the

Great War—a fact redounding much to the credit of the prophet's hydropathic knowledge, more, in fact, than to his thaumaturgic powers 'Lepra' in Hippocrates' day implied a scaly affection of the skin and this word was employed as the Greek equivalent for *zaraath* when, about the middle of the second century B C, Jewish writings were translated into that language It is doubtful whether any true leprosy was present in Greece in the time of Hippocrates (460–370 B C), though a quarter of a century later (345 B C) references to it are to be found in Aristotle There may have been cases of leprosy here and there among the Greeks earlier than this if we agree with those who regard as potent factors of spread in the early days Cambyses' expedition for the conquest of Egypt (in 525 B C) or the conquests of Darius in the same century and the march of Xerxes in 480 B C In this year, Herodotus tells us, Xerxes led 6,000,000 people into Egypt from all nations of Asia and Africa and on his retirement left thousands behind

When, however, true leprosy appeared in Greece the term used was not 'lepra' but 'elephantiasis' and the common name for some years afterwards was *elephantiasis Græcorum* In Arabic writings the word 'djudsum' was used for leprosy and Constantine of Carthage in the tenth century A D, when translating these writings into Greek, discarded the old term 'elephantiasis Græcorum' and used 'lepra' and this has persisted We must bear this in mind—that the term is a comprehensive one, including, perhaps, not only psoriasis but other cutaneous affections, scabies, eczema, and also, it may be, scrofula, lupus and even venereal disease—when we attempt to interpret the significance of 'lepra'

In Roman writings we do not meet with the disease till the return of Pompey's soldiers from the east in 62 B C, though it occurs frequently after this It is to the Romans that is owed its introduction to other parts of Europe, to Germany in A D 180, according to Galen, and Virchow avers that by A D 600 there were "hundreds of leper houses in Italy and Germany" In the fifth and sixth centuries the troops spread the infection into Spain and the extension was further assisted by the conquest of Alaric after the fall of Rome From Spain the disease was introduced into France by the Saracens invading that country in the eighth century

We shall speak in more detail later of the history of the introduction and spread of the disease in different countries, here we may summarize one or two of the main features Leprosy was almost certainly brought to Britain by the Romans The first known leper house was established at Nottingham in the seventh

century. In the thirteenth century Norway, Denmark, Sweden, Iceland, Greenland, the Shetlands and the Faroe Islands, Holland, Russia and the Baltic countries generally all had lepers. The prevalence seems to have reached its height in Western Europe about A D 1200, but was common for the next 200 years, during and after which it declined and by the seventeenth century had almost died out. Now, the disease is mainly tropical and its history is one of endemicity in certain parts—Africa, India, China—with long epidemic periods in countries where it is introduced, dying out in them for no obvious reason. By the sixteenth century it had almost disappeared from Italy, in France it persisted for another hundred years, still longer in Switzerland, the Netherlands, Germany, Denmark and Great Britain had but few cases even in the seventeenth century, the Shetlands and Faroe were not quite free by the eighteenth. It was still common in Sweden at the beginning of the nineteenth, though less, it was still not uncommon in Spain and Portugal in the early years of the nineteenth and in Norway was actually on the increase in the middle of that century.

Even at the present day the less experienced practitioners find difficulty at times in differentiating leprosy from a number of other conditions, for example some forms of syphilis, tuberculosis, lupus erythematosus, erythema nodosum, tinea circinata, pityriasis versicolor, Morvan's disease (syngomyelia), leucoderma and psoriasis have already been mentioned. Pellagra is yet another and in fact a hundred years ago pellagra in Rumania went by the name of 'epidemic leprosy'.

If at the present day confusion may arise we may regard it as certain that it was no less centuries ago when medical science was much more crude and undeveloped. In short, the term 'lepra' does not convey to us the same meaning as it did to the authors and readers of the earlier writings. Even up to the sixteenth century and after almost any cutaneous disease characterized by scaly eruption or ulceration might be included in the term. W P MacArthur has said that in old English writings we find it synonymous with *hreoſla* or scurf. Even more, it might be used as a generic term for infective disease, as in the *Annals of Clonmacnoise*, where occur the words "the leprosy that is called small-pox" and "the word 'afflicted' in Isaiah is rendered 'leprous' even to the time of Wyclif". Animal diseases were not excluded, "the leprosie or universall manginnesse" occurs in a treatise on equine diseases. In another place it is used for plague. Thus

the Black Death (see Chapter XII) broke out in England in August 1348. The following year when England was prostrated by its ravages the Scots assembled in Selkirk forest to assault the English. Plague spread north and about 5000 of the Scottish troops died of it, "a disaster which effectively cooled their warlike ardour." In the contemporary record, *Chronicon Galfridi le Baker*, this outbreak, recognized as plague at the time, is called 'lepra'. Other peculiar (at least peculiar to us now) uses of the word are the following applied to grain and the effect of meat respectively "Myst and fog make the grain leprous," and "Olde beefe doth engender melancolye and leprouse humours."

The alternative word 'lazar' is derived, of course, from Lazarus, a man covered with sores, and the term includes many diseases, but Gilbertus Anglicus and other fourteenth-century writers described a condition associated with anæsthetic patches, disfigurements and raucous voice, moreover, pictures by mediæval artists demonstrate that among them true leprosy did exist.

One would think we could infer, when we read of the large number of 'leper' or 'lazar' houses in a country, that cases would be numerous and the disease rife there, but it is not so. As General MacArthur has pointed out, citing it as an instance of history in the making, the original Erse word 'derthightibh' means 'oratories'. O'Connor, when translating this into Latin, used the word 'nosocomia,' that is 'hospitals,' and Belcher when rendering this into English added the gloss 'Leper houses,' and in a Roman Catholic country 'leper houses' became, by translation errors, as numerous as oratories.

W. P. MacArthur in his "Notes on Old-time Leprosy in England and Ireland" (*Jour. Roy. Army Med. Corps*, 1925) remarks that the mere label 'leper hospital' attached to an institution is no proof that it ever contained a single leper. Yet some establishments are claimed to have been lazarus-houses on no better evidence than a gossiping remark by some writer, perhaps years after the supposed leper-hospital had ceased to exist.

France is said to have had 2000 leper-houses in mediæval times. If this were actually so, hospitals, hospices, alms-houses must have been fully fifty times as many. C. Creighton states in H. D. Traill's *Social Life in England* (1893)

There might have been a leper in a village here and there, one or two in a market town, a dozen or more in a city, a score or so in a whole diocese. Thus, in the records of the city of Gloucester, under date 20th October, 1273, three persons are mentioned by name—a man and two women—as being leprous and as dwelling within the town to the great hurt and prejudice of the inhabitants.

To assert that "leprosy in medieval England was a more terrible scourge than plague" is nothing short of ludicrous (MacArthur)

2 ORIGIN AND PREVALENCE IN DIFFERENT COUNTRIES

Before describing these in the individual countries we may preface our remarks by stating the well-known fact that extension over the world generally has occurred through immigration and the only European countries free from indigenous leprosy are those in the temperate zone where advances in sanitation, general civilizing influences and nutrition have been carried out. We shall see how Chinese immigrants brought the disease to Indo-China, Siam, Java, Sumatra, Borneo, the Philippines and Malaya, how colonists from Spain and Portugal and infected negro slaves brought infection to the western hemisphere, for there is no evidence (see later) of leprosy there before the arrival of Europeans and the early discoverers came from Europe at a time when the disease was rife in Spain and Portugal.

Although the present work is concerned with the evolution of tropical medicine, when dealing with a disease such as leprosy, now mainly tropical and subtropical but formerly occurring in temperate and cold climates also, we cannot give an adequate account of its history if we confine our remarks to the condition in warm climates. We will, therefore, consider the origin and prevalence of the disease first in our own country and then, proceeding eastwards, state what facts are ascertainable in the various countries traversed.

1 *Great Britain*

The opinion has been widely held, and many uphold even to-day, that leprosy was first brought to England by the Crusaders, who left in 1095 and returned about three years later. This is disproved by the fact that prior to this leper-houses existed in England. The first of these is said to have been established in Nottingham as long ago as the seventh century, and there were three famous houses in existence before the crusades, namely, one in Canterbury in 1089 and others at Northampton and Chatham soon after. In Ireland leper-houses existed in 869 and in Wales in A.D. 950.

Restrictions in the early days were few and certainly not irksome. Lepers were allowed to see friends, those who lived in the neighbourhood returned home in the evening, those coming

from a distance often stayed all night in the hospital. By the end of the thirteenth and beginning of the fourteenth centuries these houses had been multiplied enormously. The *Leprosy Review* (April 1936) gives a list of forty established in 1307 in Devon and Cornwall alone.

There is no doubt that the number of lepers in England increased greatly after the time of the return of the Crusaders, for a hundred years later, at a synod held at Westminster in A.D. 1200, the Archbishop of Canterbury stated that the lepers were so numerous that they might build a church of their own, with its churchyard. This, however, they were too poor to do and a compromise was effected by provision of *hagioscopes* or 'squint windows' so that lepers attending service would not be injurious to the healthy churchgoers.

It is not a matter for wonder that they were poor, for a leper had no common law rights, he could neither make a will nor inherit property, in short he was 'dead in the eye of the law,' and in some cases when he was consigned to a leper hospital it has been stated (though the authority is never quoted) that the ceremonial for burial of the dead was performed.

The nearest approach to this which we have been able to find is the detail of the clerical ritual of exclusion of lepers from the general community recorded by R. M. Clay in *Mediæval Hospitals of England* (1909) which is quoted by C. G. Lambie (see the *Medical Journal of Australia* 1938, June 4, Vol. 1, No. 23, pp. 957-8).

First of all the sick man or the leper, clad in a cloak and in his usual dress, being in his house, ought to have notice of the coming of the priest, who is on his way to the house to lead him to the church, and must in that guise wait for him. For the priest, vested in surplice and stole, with the cross going before, makes his way to the sick man's house and addresses him with comforting words, pointing out and proving that if he bless and praise God, and bear his sickness patiently, he may have a sure and certain hope that though he be sick in body he may be whole in soul and may reach the home of everlasting welfare. And here, with other words suitable to the occasion, let the priest lead the leper to the church, when he has sprinkled him with holy water, the cross going before, the priest following, and last of all the sick man. Within the church, let a black cloth, if it could be had, be set upon two trestles, at some distance apart, before the altar, and let the sick man take his place on bended knees beneath it between the trestles, after the manner of a dead man, although by the grace of God he yet lives in body and spirit, and in this position let him devoutly hear mass. When this is finished and he has been sprinkled with holy water, he must be led with the cross through the presbytery to a spot where a pause must be made. When a spot is reached the priest shall counsel him out of Holy Scripture, saying "Remember thine end

and thou shalt never do amiss Whence Augustine says 'He readily esteems all things lightly, who ever bears in mind that he will die'' The priest then with a spade casts earth on each of his feet, saying "Be thou dead to the world, but alive again with God" And he comforts him and strengthens him to endure with the words of Isaiah "Truly he hath borne our griefs and carried our sorrows, yet we did esteem him as a leper, smitten of God and afflicted" (Isaiah lxi 4)¹ Let him say also If in weakness of body by means of suffering thou art made like unto Christ, thou mayest surely hope that thou wilt arise in spirit with God May the Most High grant this to thee, remembering thee among the faithful ones in the book of life" It is to be noted that the priest must lead him to the church, from the church to his house, as a dead man, chanting the *Responsorium Libera me Domine* in such wise that the sick man is covered with a black cloth When leaving the church after mass, the priest ought to stand at the door to sprinkle him with holy water, and he ought to commend him to the care of the people Beforehand, the sick man ought to make his confession in the church, and never again When he has come into the open fields he ends by imposing prohibitions upon him in the following manner "I forbid you ever to enter church, or go into a market, or mill or bake house, or visit any assemblies of people Also I forbid you ever to wash your hands or any of your belongings in spring or stream of water of any kind, and if you are thirsty you must drink water from your cup or some other vessel Also I forbid you ever hence forth to go out without your leper's dress, that you may be recognized by others, and you must not go outside your house unshod Also I forbid you, wherever you may be, to touch anything which you may wish to buy, otherwise than with a rod or staff to show what you want Also I forbid you ever henceforth to enter taverns or other houses if you wish to buy wine, and take care even that what they give you they put into your cup Also I forbid you to have intercourse with any woman except with your own wife Also I command you when you are on a journey not to return an answer to anyone who questions you, till you have gone off the road to leeward, so that he may take no harm from you, and that you never go through a narrow lane lest you should meet someone Also I charge you if need require you to pass over some toll way (*pedagium*), through rough ground or elsewhere that you touch no posts or things whereby you cross till you have first put on your gloves Also I forbid you to touch infants or young folk, whosoever they may be, or to give them or to others any of your possessions Also I forbid you henceforth to eat or drink in any company except that of lepers And know that when you die, you will be buried in your own house, unless it be, by permission obtained beforehand, in the church" And note that before he enters his house he ought to have a coat and shoes of fur, his own plain shoes and his signal the clapper, a hood and a cloak, a pair of sheets, a cup, a funnel, a girdle, a small knife, and a plate His house ought to be small, with a well, a couch furnished with coverlets, a pillow, a chest, a table, a seat, a candlestick, a shovel, a pot and other

¹ The biblical quotations in this office are not from the Authorized Version

useful articles When all is complete the priest must point out to him the ten rules which he has made for him and let him live on earth in peace with his neighbour Next must be pointed out to him the ten commandments of God, that he may live in heaven with the saints, and the priest repeats them to him in the presence of the people And let the priest also point out to him that every day each faithful Christian is bound to say devoutly the *Paternoster*, *Ave Maria*, *Credo in Deum*, and *Credo in Spiritus*, and to protect himself with the sign of the cross, saying often "benedicite" When the priest leaves him, he says "Worship God and give thanks to God Have patience and the Lord will be with thee Amen"

In England lepers were allowed to attend markets and to beg in Scotland they were not They were, however, not very carefully tended, a rule was made that tainted salmon or pork was to be sent to the local leper hospital, if there was no such hospital the food was to be destroyed The same applied when a wild beast was found dead or wounded in the forest

Gilbert writing in A D 1270, and John of Gaddesden in 1307-25 among others confirmed the presence of elephantiasis Græcorum—a contagious disease, the face of the patient deformed with tubercles, the skin thick, wrinkled, rough and divested of hair, voice harsh and loss of feeling in the extremities Nevertheless, we repeat, other diseases than leprosy were included under the term and almost anyone with severe eruption or ulceration of the skin would be received into leper hospitals

Lepers were more or less under the special care of the Church and measures taken on their behalf were ecclesiastical rather than medical Hence, leper hospitals were ecclesiastical institutions, of the nature of refuges, not hospitals in the sense of being places for medical treatment, and the inmates were not confined there but could go in and out, to markets and fairs Many of these hospitals, or rather hostels, were mixed, thus in 1145 there was one at Lynn for twelve brethren or sisters, nine of whom should be whole and three leprous, at St Leonard's, Lancaster, nine of whom three might be leprous It is true that, though the restrictions on their movements were slight, the public were averse to contact with them, partly because they were unsightly, partly because of their supposed infectivity, partly through superstition Accordingly, though not segregated, they were shunned and lived much in solitude They might, indeed, refuse to be isolated and the punishment for contumacious behaviour on the part of an inmate of a leper hospital was expulsion In thus depriving him of the comforts, if any, of the hospital, the law drove him into the world and many of them were wandering at will in London

The edict of 1346 which decreed expulsion of lepers from London, indicates clearly that the ' absolute and strict segregation ' which some modern writers allege to have been the hard fate of lepers in the Middle Ages was not in fact the true state of things. The preamble of the Edict declares *inter alia* that the lepers

by carnal intercourse with women in stews do so taint persons who are sound, both male and female, to the great injury of the people dwelling in the city aforesaid, and the manifest peril of other persons to the same city resorting.

Subsequent to this several expulsion orders were issued at intervals, each proving that its predecessor had failed to accomplish the object in view.

If the presence and number of leper-houses were any criterion of local prevalence, we may note that leprosaria were in existence in East Anglia, Kent, Cambridgeshire, Cornwall and the Lowlands of Scotland, but not, or very rare, in Wales, the Lake District, and the highlands of Scotland. "The Normans lived in close, ill-ventilated hovels, on a poor diet, and were very intemperate and their morals generally low," hence plague, pestilence [including leprosy] and famine were common.

Statistics are lacking and direct evidence is, therefore, not available, but there seems to have been a distinct decline in the prevalence of leprosy from the end of the fourteenth century. Again, leprosy was less commonly diagnosed as syphilis became more widely known. Also doubt was spreading and patients were diagnosed sometimes as suffering from ' temporary leprosy ' and medical men claimed to cure lepers by application of sulphur and mercury unguents.

We must bear in mind also that much of the diagnosis was left, not merely to non-medical persons, but to the untrained and even uneducated, gate-porters, hostel attendants, priests and monks were often the final judges in suspected cases of those applying for admission. When we come to the sixteenth century cases are much fewer. Many of the leper hospitals were suppressed between 1530 and 1540 at the time of the Dissolution of the Monasteries, because they were no longer needed, and in the reign of Edward VI a Royal Commission was appointed to inquire into the state of those still remaining and the report, furnished in 1547, stated that most of the leper-houses in England were empty. Belief in the disease being of supernatural origin and not amenable to medical treatment persisted, for as late as 1597 in a trial for witchcraft at Edinburgh one of the accusations was that the woman " affirmed she could haill leprosie, quhilk the maist expert

men in medicine are not able to do" (Pitcairn's *Criminal Trials in Scotland*) At the beginning of the following century the disease was of rare occurrence in England and becoming extinct as an endemic disease except in the northern islands, Shetlands, Orkneys, Faroe and St Kilda, though occasional cases were reported in the late eighteenth and nineteenth centuries, and as late as 1925 Dr J M H McLeod recorded three contact cases in the British Isles, one a conjugal case, one a boy of fifteen years who slept with a brother suffering from nodular leprosy, and the third in Ireland, a boy of twelve years who had acquired the infection from his father, a poor Russian refugee with nodular leprosy in an advanced stage

As to the causes of the decline of leprosy in Britain we can do little more than speculate During the time it prevailed conditions were little different from those of other European towns

The streets were unpaved and ill-constructed, every sort of filthiness was permitted to be thrown into the streets and remain there, vaults and common sewers were seldom adopted and the drains were above ground, the office and duty of scavengers was imperfectly executed or neglected, the supply of water was deficient and the narrowness of the streets prevented any free circulation of air In all the large towns it is not to be wondered at that pestilence and plague raged every year In the houses, overcrowding, no cleanliness, no ventilation The houses of the people were wooden or mud houses, small and dirty, without drainage or ventilation and, as Erasmus states in a letter to Wolsey, the floors of earth and clay were covered with rushes, straw and other rubbish, which were occasionally renewed, but underneath lay unmolested an ancient collection of beer, grease, fragments of fish, spittle, the excrement of dogs and cats, and everything that is nasty

Insufficiency of ordinary food, lack of vegetables, unwashed state of the bodies, sleeping at night in clothes worn during the day, the total neglect of all hygienic and sanitary laws, made cutaneous disease appallingly common It is recorded that even in 1509 King Henry's Queen, Katharine, could not procure a salad till the King sent to the Netherlands and engaged a gardener to come over and grow the necessary articles here The art of gardening was in fact introduced that year, just a hundred years after England had to send to the Baltic for corn

There is no doubt that no single factor can be pointed to as bringing about the disappearance of leprosy from England Several causes have been assigned, each of which may have played a part The first of these was the Black Death of 1348 which is said to have killed off 2,000,000 or nearly half the population, next, the

food supply improved Creighton records eleven great famines in the twelfth century, six in the thirteenth and one in the fourteenth (in 1316) Thirdly, people began to move into the suburbs of the large towns instead of all coming into the towns for protection In Tudor times besides better housing, trade improved and more and better food was purchased Fourthly, regulations for isolation have been debited with the decline, but, as has been seen, if they played a part, it was probably only a small part. In spite of the enactment *De leproso amovendo* of A D 1100 and establishments for segregation these latter did not fulfil their purpose As far as historic evidence goes strict segregation was never carried out in England.

The Writ *De Leproso amovendo* lieth, where a man is a Lazar or a Leper, and is dwelling in any Town, and he will come into the Church, or amongst his Neighbours, where they are assembled, to talk with them, to their Annoyance and Disturbance,—then he or they may sue forth that Writ for to remove him from their Company But it seemeth, if a Man be a Leper or a Lazar, and will keep himself within his House, and will not converse with his Neighbours, that then he shall not be moved out of his House But there are divers Manners of Lepers, but it seemeth that the Writ is for those Lepers who appear to the Sight of all Men that they are Lepers by their Voice, and their Sores, and the Putrefaction of their Flesh, and by the Smell of them (*Natura Brevium*, by Fitzherbert, a judge in Henry VIII's reign)

Finally, we must not forget the unexplained 'curve of prevalence' of infective diseases Leprosy was rife from the eleventh to the fourteenth centuries, plague from the fourteenth to the seventeenth, smallpox and typhus in the seventeenth, eighteenth and early nineteenth centuries, cholera later in the nineteenth and so on

As Rogers and Mur have stated, the decline of leprosy in Europe during the fourteenth and fifteenth centuries is perhaps the most remarkable feature in the history of the disease and the cause has been the subject of much discussion Munro says that the decline was most rapid in England because segregation was more strict there Lepers were driven out of London in 1346 and had almost disappeared early in the sixteenth century, though, according to Liveing, they lingered in northern Scotland to the beginning of the nineteenth

2 Europe

Before describing the history and prevalence of leprosy in the different countries on the Continent of Europe a few preliminary remarks will help to clear the ground There is no proof of the

presence of this disease in Europe before the century preceding the Christian era, but by the eighth century A D it had become sufficiently diffuse for precautions to be taken and enactments made regulating the marriage of lepers, and appointing places for their reception. The increase in the number of leper houses was rapid, it is said that by the twelfth century there were 2000 of them in France alone (but see above, p 573). After that time there was undoubtedly confusion between leprosy and syphilis as there had been probably for centuries elsewhere confusion with cutaneous affections of various kinds. Certain it is that in the fifteenth century when the characters of syphilis became more known and distinguished from other diseases the numbers of lepers fell rapidly. At an inspection of the overcrowded lazaret-houses in France and Italy at the beginning of the sixteenth century, according to Frascatorius, only a minority among those showing skin lesions were found to be cases of true leprosy.

To proceed with our discussion of the disease in Europe

(1) *Iceland* Leprosy existed here many centuries ago, some maintain that it was present there in the twelfth century and perhaps even earlier, others that it was brought from Norway some time in the thirteenth century, after the Crusades. According to Ehlers there is no evidence of its existence in Iceland, Norway or Denmark before the end of the twelfth century. By the middle of the sixteenth it had become so prevalent that the Government decided to build hospitals for them and—the Government of those times seems to have moved even less quickly than in the present—a hundred years later four buildings were constructed which were called leper asylums but were “miserable huts more like pigsties and cowhouses than sick-chambers,” says Ehlers. Spread of the infection was checked by epidemic disease from time to time, as by the ‘black death’ in 1413, an outbreak of measles in 1644, and the smallpox epidemic of 1707. This last was started by an Icelander who died abroad, it is said. His clothes were sent home and his sister wore one of his shirts, caught the infection and from her it spread all over the country and 18,000 are said to have perished, among them many lepers and their families. In 1846 there was another extensive epidemic of measles and many lepers died, the survivors, it is reported, numbered only sixty-six. Two years later the four asylums were abolished. Other epidemics in the interval, namely scarlet fever in 1797 and again in 1827, and whooping-cough in 1825 and 1839, had also carried off some of the lepers.

Throughout the middle and latter part of the nineteenth century the prevalence was decreasing. The reasons for this are not known, for there was no segregation or isolation and no treatment attempted. In 1869 a survey was made and three-fourths of the lepers were found to be on the south-west coast, it was here probably that the disease was first imported, and here also was the place where most traffic with foreigners was carried on. In 1889 another survey was undertaken and this revealed that the numbers were much greater than had been reported and far in excess of what were believed to exist. Many had been concealed because the relatives regarded it as a disgrace. Lepers were forbidden to marry, so many in an early stage married before the signs became too evident. During the preceding forty years, that is since the abolition of the asylums, the lepers had had to fend for themselves or rely on help as beggars, and it was noticed that "where the disease is considered contagious and inheritable, incidence is declining, where the people are careless and indifferent it is increasing." Though the leper asylums did little to benefit the inmates their abolition was a mistake because they served as constant reminders that the disease was not a matter to be disregarded. When lepers were allowed to wander about unhindered and as means of communication became easier it is not to be wondered at that the subsequent survey revealed an increased prevalence.

The conditions under which the poorer persons lived were conducive to intimacy and spread of any infection. The dwellings were mostly sod-huts of green turf, erected merely on the ground, with no real foundation, few of the rooms were boarded, the turf absorbed moisture and became like a soaked sponge. Windows were few, the openings were nailed up in winter, stopping all ventilation. In some the peasant and his wife would have a separate bedroom, but among the poorer all the people on the farm—men, women and children—might sleep in one room, and they also took their meals there. The beds were merely wooden boxes large enough to accommodate (!) two or three sleeping head to feet. The air consequently was foul and unwholesome, cats, dogs and children would play and lie on the dirty, leaking floor, "exchanging caresses and echinococci." In the corner would stand a bucket which received the urine of all the inhabitants and nothing was thrown away, for this "was considered good for washing wool." The food of the poor consisted largely of dried cods' heads and halibut which were hung up to dry next to wet stockings and woollen shirts. Ehlers inquired into the his-

tories of a hundred and two lepers and in fifty-one instances other cases had occurred in the same family

After 1897 measures of segregation were applied and a rapid decrease in fresh infections was observed

Of the disease in other of the colder countries of Europe we will not speak in detail, such is not within the scope of our subject. Suffice it to say that in *Norway*, where it has been seen in quite recent times, there were 2847 known cases in 1856, a very slow decline during the next twelve years, then more rapid and particularly so after 1885 when compulsory segregation of patients and other prophylactic measures were taken in hand

In *Russia* leprosy used to go by the name of the "Crimean disease", it was widespread in the neighbourhood of the Black Sea and the Sea of Azov, extending to the Caspian and the Transcaucasus. On the right bank of the Volga it was regarded by the Cossacks as contagious and isolation was enforced, on the left bank no measures were taken. Consequently, the disease has practically disappeared from the former, while persisting in the latter

(*n*) *Spain and Portugal* In Spain, though cases were said not to be very numerous, the disease was thought to be widespread in the coastal districts of Galicia on the north-west, of Andalusia on the south and Valencia on the east. At the beginning of the present century there were some 200 lepers in Teneriffe and fifty in the Leper Hospital, Las Palmas, others were allowed to wander unmolested

Portugal has furnished no reliable figures, but was probably infected to about the same degree as Spain (Rogers and Muir)

Madeira was not inhabited till the Portuguese occupied it in 1419, emigrants then came over and many criminals and outcasts, and leprosy gained a foothold. In 1500 a lazarette was established for *poor* lepers who were compelled to go thither. Since 1860, however, there has been no restraint. The people generally do not there regard it as communicable but ascribe it to a certain vegetable, and live in ordinary contact with the sufferers. Cases do not appear to be numerous, towards the end of the nineteenth century out of a population of 130,000 about two-thirds, 80,000, lived in poverty, crowded and in close contact, yet there were said to be less than a hundred lepers

(*m*) *Italy* during the present century had indigenous cases in several provinces and also others among immigrants returning from Brazil and other parts of South America. The introduction

of the disease by Pompey's soldiers in 62 B C has been mentioned above. As late as 1891 Zambaco spoke of the presence of leprosy at Scutari, where the disease was generally ignored. This author writes in his *Voyages chez les Léproux*

J'ai dû entrer dans tous ces détails pour prouver que l'isolement des lépreux de Scutari est absolument illusoire et que la population de la capitale, de Scutari surtout, se trouve en communication quotidienne, permanente, avec les lépreux, d'une manière directe et indirecte. Hé bien ! Il n'y a point de lépreux dans la ville de Scutari. De mémoire de l'homme, il n'en a point eu.

(iv) *Crete* Leprosy is believed to have been introduced into this island by the Phœnicians and thus to have been endemic there for centuries. It is often instanced as a place where measures of segregation have failed, but inquiry shows that it has never been properly put into force. Though nominally segregated, lepers have been allowed to support themselves by begging, they wander practically unchecked throughout the country and when they leave their homes it is not unusual for them to rent them to others.

3 *Africa*

We have already mentioned Africa as being the probable original home of leprosy. Coming to later times—the middle of last century—the disease was known to be common in *West Africa*, on the coast and in the interior of Senegambia, Sierra Leone, the Gold Coast, the Benin districts, the Niger and the Gaboon countries. The rates of infection in Equatorial Africa are believed to be the highest in the world, towards the end of the century the figures were given as 60.7 in the French Ivory Coast, 130 in the Ebolawa district, 20 in the Cameroons, 13 in French Equatorial Africa, 5 in French Guinea and 5.2 in Northern Nigeria per mille.

As regards the *Congo* we have no reliable information. It is the general belief that West Africa became infected by slaves or immigrants from the Sudan, and the disease has spread widely in Africa with opening up of the interior and increase of commerce.

While the incidence is comparatively light in the dry sub-tropical northern area and in the very dry German South-west Africa and British Somaliland, the central tropical belt shows the heaviest and most extensively and severely affected tract of country in the world, and one which, on account of the uncivilized and backward races inhabiting it, is likely for many years to come to be a very unfavourable field for both prophylactic and curative measures. Fortunately there is now little immigration of the leprosy-infected dark races of Africa, such as carried the disease to the Western Hemisphere during the prevalence of the slave trade, while, with the exception of North

Nigeria, the population of tropical Africa is far less than that of leprosy-infected India and China, so there is little doubt that the total number of cases is less in Africa than in Asia. In South Africa the disease is also widespread, although with a lower incidence than in Central Africa, while the conditions are far more favourable for the control of the disease in the politically more advanced Southern area where much is now being done to deal with the scourge, which should be largely controllable in our present state of knowledge (Rogers and Muir, 1925).

There is no mention of the disease in *South Africa* before the middle of the eighteenth century when it was found among the Hottentots and Bantus, but not, it would seem, among the Basutos, it certainly existed among the former before the advent of the white man. In 1756 the Governor of Cape Colony appointed two medical men to investigate the prevalence. They reported that they had not found many cases, but that since the inhabitants thought little of it they suggested the issue of a warning as to its dangerous and contagious nature. During the next fifty years little was done and the disease was found to be common in the Hottentots. In 1817 a colony was established at Hemel-en-Aarde (Heaven and Earth) in Caledon Mountains, and looked after by Moravian missionaries. The soil proved to be fertile, the climate warm and equable and water plentiful, hence the barren waste acted up to its name. All lepers in Cape Colony were drafted there, and for those having to make a long journey temporary lazarettes were set up *en route*. In the period between this and 1845 more than 400 were admitted, but by that time the authorities decided that the place was too remote for medical assistance and too far from the seat of Government, so an asylum was opened on Robben Island.

Basutoland is believed to have become infected by the Hottentots in 1835 and it was called "Lefer le Bova" or Bushman's disease. Another source whence the Basutos contracted it was from their fellow-workers in the Kimberley mines whence they transferred the infection to their homes. Immigrant colonial farmers brought it into the Orange Free State. It was already present among the Transvaal natives when the Boers formed the Transvaal Republic in 1835 and a hospital for them had existed for a long time near Pretoria. Introduction of the disease into Natal is ascribed to two men who went thence to Grahamstown, Cape Colony, and lived with a leper woman, contracted the infection and returned to Natal in 1843.

In 1863 the Hottentots were moved to East Griqualand and infected this part of the country, especially the Kokstad district. In 1883 a Commission was appointed which found that the disease

was extensively prevalent, not only among the natives but among the whites also. It was seen in Cape Colony, Basutoland, Orange Free State, Bechuanaland, the Transvaal, Natal, Zululand and Swaziland. The Commission stated that the disease could be "stamped out by proper measures energetically and efficiently carried out," by which they implied compulsory segregation. By the end of the nineteenth century Cape Colony, Orange River Colony, Natal and Bechuanaland had each adopted measures of segregation.

The latest returns from the African colonies give the following information. In Nigeria in 1934 there was an average of 4667 lepers under treatment at the various settlements, 2909 in the Southern and 1758 in the Northern Provinces. During 1935 a new leper colony, supported entirely by the Kano Native Administration, was opened at Sunaila. There are now eight Government treatment colonies in the Southern and seven in the northern Provinces, while Medical Missions support four in the former and three in the latter. As regards the Gold Coast, the latest obtainable details are those of 1931 when there were said to be 5000 lepers in the Colony, there are five leper settlements, the largest at Ho where there are over 300 inmates. In Sierra Leone there were approximately 3600 known cases in 1935, 245 fresh ones being reported during that year. Only a few cases are recorded in the Gambia, namely 275 at Georgetown and 50 at Bathurst, but many more are believed to exist. Co-operation with the Chief Headmen was obtained for erecting a leper colony in Kesseri-Kunda Province.

As regards *East Africa*, reports from Kenya do not give very definite information, some 400-500 patients received treatment during 1935, but many more are seen at the out-dispensaries—"a thousand in one district alone"—and many more never come to notice at all. In Uganda 1445 lepers were treated in 1935 at Government hospitals, but attendance is very irregular and little improvement can, therefore, be recorded. In addition Mission centres treat a large number. Thus, the Buluba, Franciscan Colony, opened in 1934, had 91 in-patients in 1935, the Nyenga Colony had 128 in-patients and 226 attending as out-patients, Bunyoni Colony of the Church Missionary Society 502 in-patients, at the Kumi Children's Home, Teso, were 220 children and five adults as in-patients and 902 out-patients, and lastly, at Ongino, Teso, were 160 residents and 628 out-patients.

In Tanganyika Territory in 1935 there were thirty-one leper settlements, eleven controlled by Government and twenty by

various Missions which receive Government assistance in drugs, equipment and money. These settlements have between 3000 and 4000 inmates. In Nyasaland lepers are treated at permanent hospitals and at rural dispensaries and there are twelve clinics administered by Missions receiving grants-in-aid. In the Zanzibar Protectorate notification is not rigorously carried out. The disease appears to be more prevalent in Pemba than in Zanzibar itself. There has been for years a leper settlement in Funzi Island, but in 1935 it was decided to close this and accommodate the lepers in village settlements on Pemba and Zanzibar Islands. Some were sent to the small colony already existing at Walezo.

There is a small camp for lepers at Berbera in Somaliland, but this will have to be enlarged before long, if mild and advanced cases are to be kept separately. In Basutoland there is a leper settlement at Maseru and the incidence of the disease seems of late years to be falling slightly, perhaps because the patients are gaining confidence and are coming forward for treatment when their disease is in an early stage. Dr Germond has been remarkably successful in inducing the patients to attend regularly and to persevere with treatment. The policy has been to aim at eliminating all possible sources of infection but there is a risk that if the recommendation of the recent Sir Alan Pim Commission is adopted, that neural cases should be treated in their houses and villages, ultimate eradication is likely to be delayed. In Bechuanaland, cases are few, probably fifty or less in 1935. There are about twice this number in Swaziland and a settlement has been established in the Mankiana district for lepers repatriated from Pretoria.

In the *Sudan* the number of lepers was estimated at the end of 1935 as nearly 11,000. About 3000 were in camps or settlements. Mongalla Province has the majority, with an estimated 7816 cases, of which a little less than half were under observation and treatment. The chief settlements are at Li Rangu, Yambio and Meridi. In Bahr-el-Ghazal Province there is a settlement at Wau and a small colony at Zalingei in Dafur Province. Incidence is less in the Northern Sudan and there is a small colony at Gedaref.

4 *India*

Leprosy is thought to have existed in India for at least 3000 years, certainly it is mentioned in Atreya's *Rig Veda Sanitá* under the name *kushta*, in the fourteenth-fifteenth century B C and from the writings of Cháraka and Sûsruta it was common in the country in the seventh century B C. In the views of some it

reached India from China, according to others from Tibet, while others again suggest Egypt. It may have been indigenous from the dawn of history. From reports and accounts of the disease in the nineteenth century A.D. we see that no part of the country is altogether free though the degree of prevalence varies greatly, being highest in Burdwan province, Bengal Presidency, in Kumaon and parts of the Bombay Presidency. It is least prevalent in the Madras Presidency. There are more actual numbers than in any other continent but the rates are lower than in tropical Africa, for example. The Leprosy Commission of 1893 estimated that there were 100,000 lepers in India, hospitals were set apart for them and they were well cared for. We must remember, however, that figures as given are probably far lower than are actually existing, for they include practically only such as are obviously recognizable by non-medical recorders, and the purdah system leads to a great discrepancy as regards the number of female cases.

5 *Ceylon*

Leprosy is common here also, especially in Colombo, Galle, Matura and Ballepittinge Provinces on the south and west, much less in the interior. Recently a survey has been undertaken (1934-5) and special leprosy registers maintained. Most were found in the Western Province and the next greatest number in Colombo. There are two large asylums, one at Hendala and one at Mantivu, for treatment of patients.

6 *Malaya*

Here leprosy has been, and is, rife, affecting more particularly the Chinese who are believed to have introduced it, especially those coming from Kwantung and Fokien. The Malays themselves are comparatively free, though, strange to say, the Sandwich Islanders, their blood relatives, are highly leprous. It has been suggested, though the grounds for the belief are not stated, that leprosy is uncommon among Malays owing to the prevalence of yaws "which tends to prevent its incidence." There is a large leper settlement at Sungei Buloh in the State of Selangor, the admission rate of patients is about 1 in 5000. This by no means represents the actual incidence in the permanent population, but the residue left by the population as it flows through Malaya. At Kuala Lumpur is an asylum which houses a number of incurable lepers who are opium smokers. These are diminishing as there have been no fresh admissions since 1931 and during 1935 they were reduced from 268 to 219.

The problem of leprosy in Malaya differs from that of most other countries because the majority of the patients are not the indigens but Chinese who entered the country already infected and year by year increase the numbers. It is difficult to arrange for their detection at ports of entry and equally difficult to accommodate them when, later, the disease becomes more obvious. At the Pulau Jerejak Settlement, Penang, among over 1000 inmates only 36 were Malays, while more than 800 were Chinese (in 1935).

In a report issued at the end of 1937 on a Health Survey of Kedah, carried out in 1935-6, hidden cases were brought to light, some in an advanced stage. Dread of segregation is undoubtedly the cause of the concealment, since the people are well acquainted with the disease and take trouble to isolate the sufferers, but the isolation is far from satisfactory. The victim is given a small hut some 6 feet square or less, without windows—little more than a kennel. Permission for home segregation is refused—if asked for—unless decent and humane conditions are provided. Comparing 1935 with 1936 the total notified (sixty-seven and sixty-three respectively) has fallen, though that of Malaya has increased from nine to twenty-seven, doubtless owing to the survey, for the preceding years show a definite increase progressively in totals, namely twenty, twenty-seven and thirty-seven in 1932-4.

In *Borneo* the disease is almost confined to the Chinese. The Chinese have visited Borneo since the fourteenth century and many settled there in the north and west and fused with the native tribes, leprosy, however, was for long unknown, for those who came were not of the coolie class, and even as recently as 1888 there were said to be no cases in the island, but two years later Chinese coolies were introduced to work on the newly opened tobacco estates, and they came from the heavily infected parts of China, Kwantung and Fokien, bringing the disease with them.

In the *Philippine Islands* the Chinese immigrants form a large section of the population, particularly in Manila, and leprosy cases were frequent in 1894 and the disease is endemic there.

7 China

Leprosy was recognized in China certainly from the sixth century before Christ, and according to some writers much earlier still. From the earliest history of the country we learn that the disease was already widespread in the basins of the Yangtse and the Yellow River, and Shantung is mentioned as a leper district in 1100 B C.

Its presence in the country has always been an important question not only for China itself but for countries outside, for wherever the Chinese immigrated—Siam, Malaya, Polynesia, Indo-China, Australia, America—they have brought the disease with them and acted as foci for extension of it. It prevails and has prevailed mostly in the hot moist southern Provinces of Kwantung and Fokien. The first reliable reports came from the Shantung Province and this has probably always been an important centre. It is a debatable question, however, whether the leprosy in South China in more modern times had any direct connection with the disease in Shantung. Most authorities think it more probable that infection of the southern provinces extended from Indo-China northwards. There was certainly every facility for spread of infection. Until quite recent years there was no systematic treatment of lepers, though the use of chaulmoogra oil for treatment was brought in over 500 years ago and is mentioned by Chu Tan Chi in the fourteenth century. The feeling towards lepers, especially to those in a late stage, was usually hostile. Again and again they were expelled from the towns, villages outside the city boundaries being assigned for them. Nonetheless they would not remain in them, but wandered about and into the towns to supplement their meagre official allowances by begging. The disease was regarded very differently in different parts of China. Thus, in southern Fukien there was no dread of infection. There was an old saying, "You may sleep in the same bed with a leper, but do not be neighbour to or cross the street to a man with itch." In the extreme west, on the other hand, the disease was much feared. If rich the leper might be burned alive, if poor he was buried alive.

The ideas of the prevalence of the disease in China only half a century ago were generally erroneous. One of the most noted textbooks of the time, Davidson's *Hygiene and Diseases of Warm Climates*, states (p. 433) "Leprosy exists throughout the whole Empire of China." So far as can be ascertained, at that time less than one-third of the country was affected. Newman in his *Prize Essay on Leprosy* (1895), quoting Doolittle's *Social Life of the Chinese*, states that there were at that time two large asylums for lepers at Tientsin, with 200 to 300 at each. Cantlie visited Tientsin in 1894 and found that there were no hospitals for lepers there. He then wrote to the resident Medical Officer at Tientsin who replied confirming what Cantlie had noticed, or rather failed to notice.

The following represents, as accurately as could be ascertained, the prevalence in different parts of China towards the end of the nineteenth century

Manchuria No indigenous leprosy, the only cases were occasional importations from Canton

Shantung Leprosy prevalent, particularly in the interior

Kiangsu Leprosy not indigenous

Hupeh Occurs in isolated foci, but the patients are not isolated and there is no dread of ordinary intercourse

Szechuen Leprosy rare, it does not follow the course of the Yangtse River

Chekiang None

Fokien Here it is a scourge, but is not much feared and many regard it as a severe and lasting form of itch, it commonly goes by the name Tai Ma, or 'Big Itch'

Kwantung is the 'cradle of leprosy,' and specially infected foci are Canton, Fatshan and Pakhoi. The first of these has a bad reputation for leprosy because the authorities have more or less segregated them there, or rather have amassed them there from other parts of the country. The original residents raised no objection to this because among the Chinese the commercial instinct is strong, and they only regarded the measure as beneficial by increasing trade. The lepers were not segregated strictly, they merely had a village life, and the place was a refuge, they were apparently unrestricted in cohabiting with the healthy, the children of the leprous and non-leprous played together, while the adults would wander about the streets and enter the shops and handle articles unrestrained.

At Macao it was not an unusual experience for thieves to raid the leper quarters at the beginning of winter and rob the patients of their blankets, there was obviously little, if any, fear of infection either by association and contact or by soiled clothing among the lower grade Chinese.

Swatow district and port were heavily infected, and from it the disease was taken and spread widely by emigrants.

Hong Kong In Hong Kong leprosy is prevalent but almost entirely imported. In 1880 lepers were few in number, living on the hill-sides above Victoria. They were uprooted and expelled to the mainland across the harbour and since then they have not been allowed to find refuge on the island. The rule has been that whenever a suspected leper is reported the police detain him until he is seen by a Government Medical Officer and if he is found leprous he is deported to the mainland. Hong Kong is a small

island and if a leper home were established there, there would be a large influx of cases. As it is the island is the first asylum sought by refugees when disturbances arise on the mainland.

Cochin-China Leprosy was widespread among the Annamites. These believed the disease to be hereditary, rules for segregation were very definite and in some parts rigorously put into practice.

The dire effects of emigrating lepers from China were evidenced in Formosa and Siam, for example. In the former the disease was very rife on the west coast where the Chinese from Fokien naturally landed, and in the latter it was the Chinese who mainly suffered, "every hamlet has its leper and every village and town its leper quarter." In Sumatra, again, the disease is common among the Chinese, though the natives are almost free from it.

Cantlie, who made a special study of the prevalence of leprosy in China, Indo-China, Malaya and Oceania towards the end of the last century, came to the following conclusions:

(1) Though hereditary transmission was not proved, its distribution in such a way was possible. He found that such was the general belief among the natives (though the lepers themselves denied it) and also that "the third generation is free from leprosy", consequently the leprous mother looking on her leprous daughter is cheered by the knowledge [should we not rather say 'belief' ?] that the children of this daughter will not be infected.

Though the belief in hereditary transmission is widely held, we must remember that in China, in those days at least, the children born of leper parents were brought up under the same conditions and often under the same roof as others, hence it would be practically impossible to separate inheritance from common source of infection.

(2) The disease may arise in a leprous country independently of personal contagion, and is, in places, feared as an inoculable disease, although Cantlie could find no proof of it. As the outcome of these beliefs some peculiar ideas and customs relative thereto are seen among the Chinese. Thus, a Chinaman will fan the seat just vacated by a leper, though he does not believe in direct infection. Infection by sexual intercourse is regarded as common knowledge and it is also believed that a leper can rid himself of the disease by sexual connection with a healthy subject (this, of course, was a common belief regarding venereal disease till quite recently even in Great Britain and perhaps is so among

certain people at the present day) Further, the Chinese believe that this procedure has also prophylactic value—a woman with a leprous husband, not herself infected, will get a healthy man to have intercourse with her, the idea being that she will thereby avert infection of herself through her leprous husband This is known as 'selling off' leprosy With this exception of sexual intercourse, one single act of which they believe is sufficient to communicate the disease, they hold that only prolonged and close contact can convey it from the sick to the healthy

(iii) The chief centres in China are the south-eastern provinces of Kwantung and Fokien

(iv) In the Far East no native race appears to have acquired leprosy except when the Chinese have settled and it may disappear, as it has done in North Borneo, says Cantlie, with departure of the Chinese coolie Hence

(v) A closer inspection of emigrants from China is advisable and deportation to the home-country is preferable to segregation in a foreign one

(vi) Susceptibility is increased [presumably he means liability to contract infection] especially by overcrowding, but also by bad general hygiene and bad feeding

In China asylums are merely refuges for lepers who are no longer able to earn a living, many of the lepers are mendicants and emerge daily from the asylums into the towns to solicit alms, and are to be found in the streets and shops, mixing freely with the rest of the people and often handling the food The general feeling is opposed to compulsory segregation

Rogers and Mur have summed up the position in Asia recently in these words

Asia shows very extensive distribution of leprosy, with high incidence in tropical areas with heavy rainfall from Bengal, Burma and Siam eastward throughout Further India and Southern China, the Philippines and in the East Indian Islands, while, owing to the extensive immigration from the South of China, the disease has been widely disseminated in the East Indies and in the islands of Oceania

8 *Australia*

For sources of information regarding the disease in Australia we are indebted, for the period between 1788 and the middle of the nineteenth century, firstly to official despatches from the Governors to the Colonial Secretary, and, for more local returns and ideas as to prevalence, to the reports of explorers and travellers and of local officials to Governors, and secondly, for the latter

half of this period, from 1820 to 1850, to statistical registers, census abstracts and abstracts of causes of death

In 1850 official medical reports began to appear and references to the disease are met with in medical literature From the last decade of the nineteenth century we have the annual reports furnished under the Leprosy Act

Cotton was cultivated in Queensland by the whites as long as the Civil War in the United States lasted, then Chinese labour was imported but was not altogether a success and they introduced leprosy In 1867 sugar growing replaced cotton and South Sea islanders (Kanakas) were brought in from the New Hebrides and the Solomon Islands, but so far as can be ascertained the Chinese were the only imported source of the disease In 1871 leprosy was prevalent in Amoy and Canton and it was from these places that Chinese immigrants came for Australia

In 1893 the disease was known to exist in the Northern parts along the Alligator River, and according to the aborigines was there before the coming of the white man The natives have no fear of it, affected members live with their families and with the rest of the tribe, share blankets and pipes, everything, in fact, is common with them and their fellows look after their leprous relations and friends, feed them and tend them when the disease has deprived them of the use of their hands

In the southern parts of the Continent, Victoria and New South Wales, there is a considerable number of cases In Victoria they were not isolated When Chinese first came to New South Wales they spread widely and engaged themselves in all sorts of duties, nevertheless, it is said that, though the disease was fairly frequently seen among the whites as early as 1868, there had been but one among the Chinese prior to 1883 It is difficult to reconcile this with the more general opinion and in fairness we must add that owing to the long latent period of leprosy it is practically impossible to separate those of the Chinese who had brought the disease with them and those who contracted it subsequent to arrival in the Colony Wherever they have settled in Australia the Chinese have lived in close quarters The recorded numbers in the earlier years of this century and later years of the preceding are certainly less than the true, for the Chinese know the symptoms well and as soon as these appear many of the patients return to their native country They have been acquainted with the disease so long and fear it so little that the healthy will associate with the sick as long as the latter are able to work and

spend their wages, it is not until they become seriously ill, or destitute and unable to help themselves, that the relatives and associates expel them from their company or report them to the police

Leprous Chinese have certainly existed in Victoria from 1858 and they continued to enter there steadily for at least twenty-five years without any restriction. In spite of this the incidence of the disease was falling in 1889, probably not on account of any preventive measures but because of their travelling to other parts of Australia. It is true that legislation was passed in 1888 giving authorities power to detain lepers, but this can have had little effect, for notification was not made compulsory till 1893

In New South Wales in 1861 one case of nervous leprosy was reported, a Chinese, but thereafter no more until 1880. Contrasting and comparing Victoria with New South Wales, Ashburton Thompson writes (in 1897)

In Victoria no cases of leprosy have been recorded among natives, but many among Chinese, in New South Wales a good many among natives who had never left the Colony in years during which only one case was recorded among the Chinese. In both Colonies the chief—in all probability the only practical—danger lay with the Chinese

The measures taken to deal with leprosy and the laws enacted against lepers in Australia differ as regards the five colonies—Western Australia, South Australia, Victoria, New South Wales, and Queensland—in date of enactment, in theoretical efficiency and in the authority appointed to carry them into effect. In 1885 there was a Parliament enactment in South Australia, applying to the whole Colony, and in 1889 in Western Australia. In 1890 one for New South Wales, the following year for Queensland (see below) and in 1893, as stated, notification was made compulsory in Victoria. For Queensland a special Leprosy Act was passed when a proclamation under the Public Health Acts had been in force for a year. In New South Wales there was no Public Health Act and in consequence a special Leprosy Act was required. In the case of the other colonies mentioned, there was merely a proclamation under the Public Health Acts empowering the Boards of Health, with the consent of the Governor in Council, to declare any disease a "dangerous infectious disease." It was this that set in motion the machinery necessary for compulsory notification and isolation.

In 1890 no cases were known in Tasmania, so no legislation was enacted as in the Australian colonies

Rogers and Muir, writing in 1925, state that

Australia shows very little [leprosy] as a whole, except in the tropical part of Queensland and in New South Wales, coloured immigrants being chiefly affected, while segregation and the repatriation of leper immigrants are being efficiently enforced

It is worthy of incidental note that it was in Melbourne that R. T. Bull in 1907 described a leprosy-like disease in the rats, exhibiting cutaneous nodules involving the subjacent muscular tissue, with tendency to superficial ulceration and patches of alopecia

9 *Pacific Islands*

We may state generally that leprosy is to be found here wherever Chinese coolies have settled. In Fiji and Samoa leprosy is now endemic, but it is of comparatively recent introduction, probably within the last fifty years. In Nauru the spread at first was slow, but became much more widespread after the influenza epidemic or rather pandemic, of 1918. Twenty per cent of the population were said to have become infected, but the form was mild and now the prevalence is definitely declining. At first, there is little doubt, introduced by the Chinese the disease is now more prevalent among the Indians. There is a Leper Hospital at Makongai, and it has been noticed that the Indians, though often in a more advanced stage of the disease than the Fijians or Chinese when first seen, react much more readily and satisfactorily to treatment. According to Rogers and Muir the natives in former days and, in fact, till comparatively recently, were reported to kill privately all lepers who showed ulcerative skin lesions and they avow that since Government put an end to this practice the disease has spread—not at all unlikely—and in the opinion of the medical officers it is thought to have increased in prevalence of late years. At the present time leprosy is to be found in all the islands of the Gilbert group, but is non-existent in the Ellice Islands.

Instances of spread of infection from a small, limited but uncontrolled focus may be cited from the extreme east of the Tuamotus of the Society group of islands on the atolls of Reao and Pakorua with populations of 340 and 200 respectively. In 1903 and 1915 two lepers were introduced, in 1937 there were 101 infected or suspected lepers in Reao and 71 in Pakorua. Three-fourths of these were under the age of fifteen years (see also Rodriguez, below, p. 606).

Hawai Captain Cook makes no mention of leprosy among the natives of these islands at the time of his discovery of them

in 1777 Later visitors speak of skin diseases of various kinds and describe cases fully, but never so much as hint at any of them being leprotic In 1848 gold was discovered in California and there was a consequent influx there of Chinese and a constant communication between Hawaii, China and California, the disease came to be named Mai Pake, or the Chinaman's disease In 1865 a hospital was provided for them near Honolulu and a segregation colony on Molokai The work of Father Damien between 1873 and 1889 is well known to all Rogers writes (1925)

The majority of cases are of the more highly infectious nodular form, as is nearly always the case during the marked increase of leprosy in any country, abundant sources of infection remained in the villages while the social conditions were most favourable to its spread, as the people had no dread of the disease, were very hospitably disposed and had no objection to sleeping and eating with lepers, or smoking the same pipe The men, women and children all lived together in one-roomed houses

By 1894 it was very prevalent Many quacks used to go there to try out their remedies for the Government would welcome any who claimed to have a cure and give him permission to try At the time Cantlie made his investigations the New Hebrides and New Britain were free from leprosy, it was rare in New Caledonia, very rare in Fiji When once introduced the disease spread rapidly, so that by 1910 the rate in New Caledonia, forty-five years after introduction by the Chinese, was 90 per mille, one of the highest in the world, in the Loyalty Islands, introduced in 1878, it was reported by Nicholas to have a rate of 35 per mille, and this was undoubtedly an underestimate, for he was well aware that many were concealed In the Marquesas Islands in 1903 the incidence was 66.7 per mille We mention these rates because they are the only figures available for those times, but we must not forget that they are often wrong and probably in most cases underestimated and fallacious, being based on the proportion of lepers found among a limited number of persons examined

There is little to tell of leprosy in the non-tropical parts of the *Western Hemisphere* Canada has few cases, except for a focus in New Brunswick among the poorer French inhabitants who had come over from Normandy Among the Chinese who have immigrated into British Columbia cases are also met with

Leprosy is believed to have been introduced into *America* from various sources—Europe, Asia, Africa and the West Indies Dr Chico, however, a Mexican authority, is of opinion that it existed in Mexico in pre-Columbian times and states that when the Spaniards

first came to Mexico in 1519 they found lepers in Anahuac and that Cortez erected the Hospital de San Lazaro for them. The majority of writers are opposed to this and believe that America was free of leprosy until it was introduced by the Spanish and Portuguese.

In the United States leprosy is endemic in the moist semi-tropical parts bordering on the Gulf of Mexico. Louisiana was probably infected by early settlers and slaves from Africa and later by Acadians from Nova Scotia in 1755 and by cases imported from the West Indian Islands in 1758. Hans Sloane saw cases in Jamaica in 1687. In 1766 Ulloa, the Spanish Governor of what is now Louisiana, began to isolate lepers at Belize, near New Orleans, and in 1778 a hospital was built at New Orleans. The disease seems to have died out early and to have been re-introduced in 1866 by French immigrants, since then it has persisted, and chiefly among the European population. In 1900 Dyer reported that the disease was increasing rapidly, chiefly in the old French section of New Orleans and that the people were totally indifferent to the danger of it.

We mentioned above that America was free from leprosy until the Spanish and Portuguese introduced it, but as soon as the slave trade became a thriving industry the negroes brought hundreds, perhaps thousands, of infected persons among them, and later again, after the time of emancipation, Chinese and Indians who took their place, introduced yet more leprosy. Generally speaking, the highest rates of incidence are to be found in the moist tropics of the northern districts of South America, especially Guiana.

Thus to *Dutch Guiana* Portuguese came with their slaves from Brazil in 1644 and a decade later slaves were being imported from Africa to work on the plantations. Cases increased in number during the ensuing fifty to seventy-five years and in 1728 lepers were forbidden to frequent the streets of the towns and in 1763 importation of lepers was prohibited. A quarter of a century later the white population was becoming increasingly affected and in consequence measures of segregation were enacted.

Much of the information regarding leprosy in Dutch Guiana we owe to Godfried Willem Schilling who left Amsterdam for Dutch Guiana in 1753 and practised for some years in Paramaribo. He made notes on his cases, and especially on skin diseases, and on returning to Holland in 1768 wrote a treatise on Leprosy, in Latin, and presented it as his M.D. thesis. Two years later he published another work on Yaws. After touring Europe he set out again for the west and was appointed Censor of the Surinam

hospital, he died in 1777 His work on Leprosy, *De Lepra Commentationes*, was edited by Johann David Hahn, and this edition was published in 1778 Schilling remarks that only those indigenous natives suffered from leprosy who had had contact with negroes from Africa, he thought that the disease was contagious, the contagium being transferred by the discharging lesions. He notes change of colour and the presence of patchy anæsthesia as early symptoms and quotes instances of conjugal infection and believes in its congenital transmission

French Guiana is believed to have become infected by slaves imported from Africa in the seventeenth century Here, as in fact in most places, attempts to deal with lepers and leprosy from the restrictive and preventive aspects have been vacillating and the execution of them weak to futility, for the past 200 years It is not surprising, therefore, that the rate has remained almost unchecked in places where sanitation was bad, overcrowding common and intercourse unrestricted In 1918 Leger estimated the incidence in French Guiana at 22 per mille, and the following year Vellet gave 16 per mille, neither probably correct

Similarly *British Guiana* owes the original introduction of the disease to African slaves Before the abolition Dutch planters were accustomed to isolate lepers, later, restrictions were removed, the disease spread and this was fostered subsequently by East Indians and Chinese labourers The latest official returns from British Guiana state that in 1935 there were 738 known cases of leprosy, of whom a little over two-fifths were inmates of the Leper Hospital, the remainder attending at one or other of the out-patient clinics, there is a home established for the children of lepers

Venezuela is thought to have been infected in 1825 by immigrants from one or other of the West Indian Islands *Colombia* first by Spaniards coming over from Andalusia and later by imported slaves from West Africa

In the *Pacific Coast States* it is the Chinese immigrants who show the heaviest incidence, thus, in California leprosy was, it would appear, introduced by Chinese and Indians brought in after abolition of the slave trade There are lepers among those who have been imported into the large cities of the Atlantic coast states, but there seems to be very slight tendency for them to act as new foci

Regarding the North Central area, New Scandinavia, Hansen states that the Norwegian lepers there lived in much more commodious houses than those in Norway, and moreover the lepers

usually occupied separate bedrooms, instead of being crowded together as this class was in European Scandinavia. It is to these better social and hygienic conditions generally that he ascribes the remarkable tendency for leprosy to die out from Norwegians living in America. It was present among Scandinavian immigrants in 1864, in Minnesota, Wisconsin and Iowa, and thirty years later Hansen stated that there had been 160 lepers in these states and thirteen were living at the time of his visit. It was clearly diminishing, as mentioned above. The first Scandinavian to become leprous had landed in 1854 and lived in Minnesota, his disease appeared ten years later and he died in 1878. Dr McCoy sums up the incidence in this State by saying that between 1856 and 1900 about fifty lepers had been introduced. From these there developed seven cases in the second generation, that is the first generation born on American soil, there was only one case in the third generation, though possibly an occasional one may have been overlooked.

No adequate explanation is forthcoming of rare cases seen, patients who give no history of contact with others or of residence in areas where this disease is endemic, e.g. one has been reported in each of the states, Virginia, Illinois, and Pennsylvania.

For a long time New York City isolated lepers on one of the islands in the East River, but as time passed the risks of spread of infection were regarded as insignificant and this isolation station was given up. Years before the establishment of the National Leprosarium at Carville, San Francisco was accustomed to isolate lepers, twenty-four or more at a time, mostly orientals, in an annexe to the City Pest House. At the present time Carville has a capacity for 400 and the population is 375. It is rather of the hospital than of the colony type.

Brazil Leprosy was not known there at the time of its discovery by the Portuguese admiral Pedro Alvares Cabral in 1500, and in letters written by Vaz Caminha that year containing many details of the country and its inhabitants there is no mention of it, nor in the writings of the Jesuits who lived there, mostly among the Indians, between 1659 and 1759. Also Gabriel Soares e Souza notes in 1587 the tendency to contraction of *bouba* (yaws?), but does not refer to leprosy. Americo Vespucci in his *Lettres de Voyage*, written the same year, does not speak of it, nor do other travellers such as Saint-Hilaire, Martius, Kuppfer, Orbigny, Peckolt or Humboldt. Even later, there is no reference to it in Piso's medical report on the country published in Holland in 1648. More recently, J. Moreira, Roquette Pinto and others have

tried to trace records of leprosy among the indigens of Pará, Amazona, Maranhão, Nambienares, da Serra do Norte, and other parts but with negative results, and de Souza-Araujo, probably the greatest authority on leprosy in Brazil, between 1917 and 1924 examined hundreds of Indians in Brazil, north and south, and in Arizona, but could find no cases of the disease Ambietta and Lafitau saw no cases among the native population of Santa Cruz, although the Jesuits lived for many years in close contact with the people

How then was it introduced, for it is common enough in certain districts now ? Some have ascribed its introduction to the slaves imported from Africa This first took place in 1583 and by the end of the sixteenth century they were numerous in Rio de Janeiro, according to Fernando Terra, and further study of the parts of the West African coast and of the interior whence the slaves were taken showed that leprosy was not common there It would seem more probable that the disease was brought over by Europeans, and in particular by the Portuguese, though Dutch, French and Spanish probably took a share in it Leprosy was common among the Portuguese in Madera as long ago as 1419 There is little doubt, however, that before long the slaves assisted and promoted the spread, and we may take it that primary introduction was by the Conquistadores of Portugal and secondary by slaves, cases began to be seen in Rio de Janeiro from A.D. 1600 onwards Leprosy is known to have been very prevalent in Portugal at the time and French mariners coming to Brazil from 1555 and for the ensuing century and a half were recruited chiefly from Pas-de-Calais, Normandy and Brittany In Normandy there were more than 450 leper asylums (we have stated above that Normandy French sailors brought the disease to Canada) In Holland, too, leprosy was prevalent—there were sixty leprosaria there—for a hundred years or more before the Dutch came to Brazil which they did in large numbers between 1624 and 1654

As the numbers of slaves increased, so did they furnish a larger and larger quota of lepers Forty-five years after their being first introduced, out of a total population of 57,500 in Brazil, 14,000 were slaves from Africa The chief ports of entry were Rio de Janeiro, Bahia and Recife, and it was there that the disease made its greatest ravages and its most rapid progress, so much so that in 1637 an appeal for control was put forward in Rio By 1710 Rio de Janeiro's population was 60,000 and half were negro slaves, by 1851 the population of the Province of Rio was 556,180, of whom

293,554 were slaves, while among the 266,466 who constituted the population of the municipality 110,602 were slaves

During the nineteenth century censuses of lepers were undertaken from time to time and nearly four-fifths (it varied between 70 and 80 per cent) of the lepers were coloured persons and 75 per cent of them were negroes

We have stated above that in 1637 a request for control measures in Rio was first put forward, but not for more than a hundred years was anything of material value carried out, although another call for control was made in 1696 In 1698 an institution was set up in Igreja de Nossa Senhora da Conceição which was used till 1740, in which year the municipality of Rio de Janeiro asked the Government that a special building might be established for lepers By that time there were 300 lepers among a population of 60,000 The appeal was made to the King of Portugal, Dom João V, through the Governor in the following year Drs Francisco Teixeira and José Rodrigues Froes in the Corte obtained an order for isolation of patients and El Conde de Bobadella, the Governor-General of Rio, had the poorer lepers concentrated in huts in S Christovam In 1744 a Royal Order was promulgated by which leprosy was to be considered a contagious disease, and it regulated the treatment of lepers especially in the early stages, the isolation of them in asylums and separation of the sexes Separation of the children from their leprous parents was advised and a rigorous selection of African immigrants In 1763 Bobadella died and his successor, Count da Cunha, transferred the lepers from their primitive huts to the Jesuit convent where a modern leprosarium now stands In 1766 a decree was passed for compulsory segregation of all lepers in a Hospital dos Lazaros This soon became overcrowded and a second hospital was erected in 1787.

In 1836 Barão de Caçapava, Governor of Pará, gave his approval to a law restricting the movements of lepers, but within two years this was considerably relaxed, in fact it almost fell into abeyance and the disease soon began to show a recrudescence, and for the next eighty years or so, till 1920, the question was left alone Then the Federal Bureau of Control was created in connection with the National Public Health Department and a census was undertaken Federal rules of prophylaxis, control and treatment were approved In consequence patients received treatment in dispensaries, had to submit to some degree of isolation, either in their homes or in asylums, sanatoria or agricultural colonies Till then there had been six leper hospitals, but subsequently there were established thirteen modern institutions of

the asylum or colony type, and some of these last comprised as many as 1600 patients

As regards prevalence at the present time there are three main foci in the north from Maranhão to Acre Territory, in the centre Minas Geraes, and in the south São Paulo. There are lepers, however, in every State and altogether the number is about seventy-five per 100,000 inhabitants

Lastly, the *West Indies*. From the historical aspect there is not much information obtainable as to the origin, course of prevalence, control measures and so forth of leprosy in the West Indian Islands. The history is in the main a repetition of what has been said regarding South America—namely, primary introduction by Europeans, Portuguese and Spaniards, as these islands became colonized, and traffic arose between the islands and the mainland, later, a wider extension of the disease by imported slaves from Africa. Cuba is believed to have been infected by immigrants from Valencia about the middle of the eighteenth century. Of leprosy in the Antilles we know little and we have no statistical figures of prevalence prior to the middle of the nineteenth century. Jamaica in 1861 had some 800 among a population of 440,000, the proportion being rather higher (forty-one among 27,000) in Kingston, in St Kitts there were in the same year forty-seven cases among a population of 24,000. Nevis and Antigua had fewer, twenty-two among 36,400. This last figure relates to the inmates of a leper-house and is probably a considerable under-estimation of the actual cases. The same applies to Trinidad where there were fifty inmates among a population of 83,000. By the end of the nineteenth century the prevalence in the Antilles generally was between one and three per thousand, and since then the disease has tended to diminish in incidence. The latest information obtainable from recent reports is below

Bahamas. Seventeen inmates at the Lazaretto, both nodular and anæsthetic types are seen, but the former predominate

Barbados. Of Barbados we have a little more information from Hughes's work, the *Natural History of Barbados*, published in 1750. Though he was unable to trace its origin he stated that it first appeared in the island "about sixty years ago" (i.e. 1690), and from 1730 till the time he was writing the disease had spread much among whites as well as blacks. He noted that children were often attacked although neither of the parents presented any signs. Whether this was due to the fact that one or other of the parents suffered from the neural form in an early stage which

had escaped recognition, or whether the children acquired it outside from nurses or other children, cannot be decided now, but it evidently struck Hughes as remarkable. The general opinion in the island was that the disease was inherited, and especially from the father, and he quotes the instance of a negro woman who, by cohabitation with a negro man, had two children, though she herself did not become infected. After some years she left this man and had children by another, but none of these developed any signs of leprosy. After an interval she returned to her old love and again was fruitful, the children of this last venture as they grew up became leprous. The story is not complete, for we are not told that the father was a leper. Also we may be allowed to wonder whether the condition may have been syphilitic, the children showing symptoms while the mother did not—a not uncommon occurrence.

The most recent figures (1935) give the population of Barbados as 184,912. At the Leper Home there were seventy-five inmates, twelve less than two years before, but five new cases had been admitted during 1935 and six who had been allowed out had to be readmitted. In addition there were sixty discharged lepers still under supervision, these are subject to certain restrictions in that they are prohibited from engaging in certain occupations where they might prove a menace to others.

Bermudas Eleven in 1933, nine in 1935 at the hospital; no new cases admitted during the year.

Jamaica The latest account (1935) states that there is a general impression of declining incidence, though in 1933 there were 128 inmates in the Lepers' Home and twenty-two fresh admissions during the year, in the following year there were thirty-four admissions and in 1935 another thirty-one.

Allowing for deaths and absconding inmates the total at the end of the year was 149. Perhaps this increase is due to more careful and earlier diagnosis of cases and not to greater prevalence. Plans are being considered for removal of the Lepers' Home at present situated in Spanish Town, the old capital, to a more suitable site and the accommodation is to be extended and modernized.

In the *Turks and Caicos Islands*, an annexe of Jamaica, there are five known cases among a population of 5612 (this was the population figure at the 1921 census, no later is available).

The Leeward Islands In *Antigua* the incidence is about 1 per mille, i.e. thirty inmates of the Leper Home, the population being 32,424, it is actually probably higher because not all cases are in the Home. In *Dominica* it is about the same, thirty-eight

patients among a population of 45,239 in 1934, thirty-three in 1935, five having died and no fresh notifications having been received. *Montserrat* is practically free, the population in 1935 was 13,246 and two cases of leprosy were reported in 1934, one an immigrant from *St Kitts*. In *St Kitts* and *Nevis* the combined population in 1935 was estimated (on the 1921 census figures) as 37,742, fifty-three lepers lived in the Leper Home. Two years before there had been fifty-one, but in the interval there had been six fresh admissions and four deaths.

Of the *Windward Islands*, *Grenada* has, it would appear, no endemic leprosy, in 1935 there were thirteen inmates at the Leper Home, the same number as in the two preceding years. Inquiry shows that in most cases these patients had acquired the infection in other countries. *St Lucia* has an average of thirty in the home, deaths and discharges about balancing new admissions. *St Vincent*, with a population of 55,219 (in 1935), has about a score of lepers in the asylum, they do not as a rule apply for admission till their disease is in an advanced stage when little can be done for them.

Trinidad and *Tobago*, with a combined population in 1935 of 439,994, have a leprosy incidence of 1 per mille, or a little over. A certain number who had been allowed out of the settlement at Chacachacare have had to be readmitted, being unable to support themselves or, owing to bad economic conditions, to be supported by their relatives. Cases numbered between four and five hundred.

CAUSES OF PREVALENCE

If we take the trouble to review and analyse the state of the inhabitants and their mode of living in the different countries where leprosy prevails, we shall be able to summarize the conditions which appear to have influenced the prevalence of the disease in the past and, in some cases, to be still active. These may be considered as subsidiary or auxiliary causes of leprosy, but are best discussed here, the history of the actual cause is considered later.

The chief of these conditions was undoubtedly the defective hygienic state maintained among people in a low condition of civilization such as characterized Europe in the Middle Ages, for example. Doubtless, too, the contrary may be affirmed, that diminution and disappearance are ascribable in great part to the steady improvement of conditions of living.

We shall see when we deal with the measures adopted to control the infection how these indications are followed up generally.

at the present day, as an essential preliminary to successful treatment, namely to improve the housing of the leper, to give him proper food, to remove all inimical influences, such as concomitant disease, syphilis, ankylostomiasis and so on, and all source of worry and anxiety, such as care for his family while he is under treatment. Specific treatment without these general measures has been found to prove disappointing, if not useless.

Secondly, as we saw in the case of Hawaii, overcrowding and disregard of the contagious infective nature of the disease, do much to promote its spread. It is recorded that the imposition of a hut-tax in Nyasaland led to overcrowding and consequent increase in the spread of leprosy (and of tuberculosis). General promiscuity might almost be included in the last, sexual promiscuity still more, we have seen how in parts of China and elsewhere there is a prevalent notion that a leper can pass on his infection and get rid of it himself by connection with a healthy subject, and how, in Honolulu for example, the spread was fostered by the fact that the people had no fear of the disease but would live, sleep with and share pipes, etc., the healthy with the leper. This has been noted in several countries, by Hill in British Guiana, by Landré in Surinam, and in the Sandwich Islands. Among the Mohammedans in Senegal, also in French Equatorial Africa, in French Guinea, Hawaii and other places where contagion is disregarded, prevalence is naturally greater (see comparison of the disease on the left and right banks of the Volga, p. 583). Rodriguez, an island near Mauritius, is a good concrete example, here, as recorded by Mangenic, leprosy was not known until one man developed it four years after his arrival there and during the ensuing forty years twenty-three cases originated from him, mostly in his own family or that of his employer.

On a larger scale we saw how in Cape Colony migration of the infected Hottentots into East Griqualand in 1863 caused spread of the disease there. We have seen also how, in Iceland and elsewhere, abolition of segregation, closing down of leper hospitals and the consequent thrusting out of the leper to mix unchecked with the healthy was followed by increase of prevalence, as would naturally be expected. We cannot hold the Royal College of Physicians blameless in this respect for their report of 1865 declaring leprosy non-infective was followed by increase in several places where this dictum was acted upon and precautions removed, as in the West Indies, St. Kitts and British Guiana, Dutch Guiana, in the Moluccas and Java.

What part climate plays is difficult to estimate. According to

Rogers places where the incidence is high, from 15 to 60 per mille, are all tropical areas with a damp climate. Where the incidence is low in tropical countries, *e.g.* British Somaliland, the west coast of Peru and others, the districts are dry though hot. It may be, as Rogers suggests, that dry heat is inimical to extracorporeal survival of the bacillus, and also insects are more common (and more voracious) in hot damp districts, this is supported by the fact that the primary site is often on some exposed part. He sums up by saying that a strongly affected belt, 500 miles wide, extends across Africa to the Egyptian Sudan and to Abyssinia. At Addis Ababa the infection rate was 20 per mille. In the sub-tropical zone, from $23\frac{1}{2}^{\circ}$ to 35° latitude, infection is widely distributed but in few places does its intensity exceed 1 per mille, Crete, Central China, Korea and Southern Japan are exceptions.

In the temperate climates, 40° latitude or more, rates of 1 to 5 per mille are more frequently found than in the subtropical zone, but infection is largely a house infection because of the cold winters and close contact, with less open-air life.

It is easy to deduce from the foregoing the conditions which would tend naturally to reduce the prevalence, we need not go into them in detail, but fear of the disease and forcible isolation, as carried out in Senegal, on the Ivory Coast, in Madagascar, more drastic the killing off of young lepers or all with ulcers, as recorded of Nyasaland and Fiji and more recently in China (see later), or excluding lepers, as from Pondoland, all would have this result, and, as mentioned above, extensive epidemics as the Black Death in 1413, smallpox in 1707, measles in Iceland in 1846 killed off lepers in large numbers and so reduced foci of infection.

3 CONTROL AND PROPHYLAXIS

The control of leprosy is as simple in theory as it is difficult in practice. The reasons for this will be obvious by comparing its essential characters with those of acute exanthemata, variola for example. Thus, the latter is highly contagious, leprosy is not, has a short incubation period, up to fourteen days, whereas that of leprosy is long, up to five years with an average of three and a half years,¹ it is very dangerous, leprosy is not, runs a

¹ Dr Hillebrand reports a case in Borneo, a European boy who used to play with a leprosy native child. The latter pricked himself with a knife in an aesthetic part and was imitated by the European lad. Shortly afterwards the latter was sent home to Holland and *nineteen years* later developed leprosy, "returning to Borneo a confirmed leper." We would like to know more details than this and to be assured that there had been no other possible source in the meantime.

short course and has a short infective period whereas the course and infectivity of leprosy are prolonged Further, smallpox is usually easily and promptly diagnosed, whereas the onset of leprosy is insidious, its diagnosis, especially the nervous form, often for some time in doubt even by a trained physician Lastly, if restrictions are made too severe, patients will make every effort to evade them and will conceal their malady, often with the help of relatives and friends

Important dates in the history of leprosy control are 1897, when an International Congress was held in Berlin, 1909, when another International Congress took place in Bergen, Norway, and 1924 when the British Empire Leprosy Relief Association was established

At the first of these a Commission of twenty was nominated to discuss the question from several aspects and make preparations to found an International Society for the extermination of leprosy and to establish 'Archives' for the study of the disease, comprising scientific, statistical and other matters At this Congress was discussed the ætiological rôle of the bacillus and the channels of infection, by clothing, common use of utensils, smoking a pipe in common, for example, also the question of infected dwellings, and the evidence in favour of skin infection by bacilli discharged from nose or mouth or ulcerous lesions Some held that the bacilli which escaped were no longer living and active

At the Second Congress in 1909 reports were received on the prevalence of the disease, on the measures in force to deal with patients and with prophylaxis as tried and carried out in different parts of the world—non-tropical as well as tropical Sessions were devoted to the reading of papers and discussion of (1) The causes and ways of spread of leprosy (2) Clinical forms and diagnosis (3) Treatment, notably by Deycke's nastin and by antileprol (4) Pathological anatomy (5) Prophylaxis and preventive campaigns

The question of treatment by drugs we defer for the present, but the general conclusions arrived at may be stated, namely (i) That leprosy is a contagious disease, (ii) Isolation of lepers in leprosy countries is recommended, (iii) Lepers should be excluded from engaging in occupations which allow of the possibility of transmission, (iv) Children of lepers should be separated from their parents and kept under supervision, (v) Those persons who have shared dwellings with lepers should be examined at intervals to detect the early signs of infection in them, (vi) Leprosy is not incurable, but no certain remedy has yet been discovered

The third of the years of historical importance in leprosy control was, as stated above, 1924, when the British Empire Leprosy Relief Association was founded in London. By its means efforts were made to get into touch with all agencies and workers whose aim was the relief of leprosy in the Empire. With a view to ascertaining what was being done in each country and how the work could best be aided the following questionnaire was prepared and widely circulated.

- 1 Name of country or area dealt with
 - (a) Area in square miles
 - (b) Population by race or religion and its distribution
 - (c) Climate and other relevant facts
- 2 Census or official rate *per mille* (If such is not available a personal estimate is requested)
- 3 What legal powers exist as regards
 - (a) Compulsory segregation
 - (b) Prohibition of occupations concerning food, clothing, and domestic service
 - (c) Repatriation of leper immigrants and those developing the disease within a given period of arrival
 - (d) How far are such powers exercised?
- 4 Give for each leper institution
 - (a) The accommodation
 - (b) Aggregate numbers of each of the last three years
 - (c) The proportion of voluntary admissions
 - (d) Can patients be detained until non-infective?
 - (e) Are members of the family of lepers examined periodically for incipient leprosy?
- 5 What are the rules regarding
 - (a) Separation of the sexes
 - (b) Marriage of lepers of reproductive age
 - (c) Cohabitation of married lepers
 - (d) Separation of lepers' children at birth
 - (e) Frequency of leprosy in separated children and their age at the time of development
 - (f) Ditto of children living with leper parents
 - (g) What is the birth rate of married lepers?
- 6 What is the staff of the institution as regards.
 - (a) Medical qualified men resident and visiting
 - (b) Nurses or attendants qualified to give remedies hypodermically. If not yet available could any be trained for such work?
- 7 What types of buildings are used and how far are they and the equipment satisfactory?
- 8 What treatments are used and how long have soluble preparations of chaulmoogra and other oils been injected, and with what results?

- 9 If the improved treatments are not yet in general use, would you give them a trial of at least one year if the Association can send supplies and directions for their use ?
- 10 Could such treatment be superintended by a competent doctor attending at least once a week, and a full report of the trial sent to the Association ?
- 11 Are lepers treated at general hospitals, and could separate out-patient leper clinics be established for early cases ?
- 12 In addition to improving treatment, in what ways could the Association best help you ?
- 13 Have you any suggestions to make regarding the proposed lines of work of the Association ?
- 14 Please supply any additional information of interest regarding the prevalence and modes of spread of leprosy
- 15 Does the indigenous population employ any special remedy against leprosy, and if so can you obtain some for investigation ?
- 16 Mention any local customs or conditions affecting leprosy work
- 17 Please state how you consider the extinction of leprosy could best be effected
- 18 What is the prospect in your area of Government and public support for an anti-leprosy campaign ?
- 19 Please give other relevant facts, if any, not covered by this questionnaire

Sir Leonard Rogers was the first Medical Secretary and the policy of the Association was, firstly, to extend the application of the improved methods of treatment as rapidly as possible throughout the Empire by supplying the latest information and most approved drugs to leper institutions, settlements and hospital clinics, and training those in charge of lepers in applying the treatment efficiently Secondly, to support sound schemes of segregation, with the best treatment, in countries where the great majority of the lepers can thus be dealt with and the disease rapidly reduced (as in the West Indies, for example) Thirdly, to collect information and statistics and to issue bulletins of information to workers among lepers Fourthly, to support further researches on both the ætiology and treatment of leprosy with a view to discovering more efficient methods of prevention, and, further, to simplify, shorten and cheapen the curative measures

It would be impossible to give in the space at our disposal an adequate account of the work done by the Association, the *Leprosy Review*, which is their official journal, is published quarterly,

contains original articles from time to time and reports of the state of the disease, its prevalence and progress in dealing with it in different parts of the globe

Coming to more specialized methods of control, we will deal first with *segregation*. From the fifteenth century and even earlier leper villages have been established in Asia and Africa, but there was no discipline, inmates could wander in and out at will and, as we have seen, it was quite customary for them to go into the towns to beg in order to obtain help and money for subsistence. Another fault was that as a rule only those in an advanced stage were sent to these villages. In China lepers were not allowed to marry except among themselves, but this restriction was not maintained beyond the fourth generation. We have seen that the idea is widespread in China that the third generation is believed to be free from inherited taint of leprosy. Nowhere would the segregation seem to have been strictly adhered to. Even as late as 1912, though many lepers in East Africa were segregated in camps and in villages, many more remained outside. In New Caledonia and other islands of Oceania the French attempted to isolate, but the results were almost nil, and the good was often more than counterbalanced. Thus, many would abscond, others would bring in the healthy members of the family to live with them. This became so common towards the end of the nineteenth century that in 1898 the plan was abandoned and the lepers were allowed to return home. The same occurred in the Loyalty Islands, in the Marquesas the results were rather better because segregation was more strictly enforced. Crete has already been spoken of (see p. 584) as a place where segregation was little short of farcical in its interpretation.

In place of segregation, in Madagascar, Malta, St. Thomas (Danish West Indies), in Russia, Rumania and parts of South Africa 'home isolation' was practised, here too the results were varied according to the type of case and the thoroughness of the control exercised. Apart from instances where the patients broke their parole certain relaxations of the rules were allowed. Thus, in Madagascar, if the patient had no open sores and if his family was willing, he was allowed to return home. An inspector visited him from time to time and at discretion could order his removal to the asylum. Others were interned, or rather housed in colonies situated at a distance from the towns. At these colonies there was land provided for cultivation, the inhabitants living, as it were, in a community of their own, having full liberty in the village,

under a leper chief, and being attended by members of an efficient medical service. As stated above those becoming bacterially negative were allowed to return home as 'temporarily cured,' but were kept under supervision and visited regularly. In the colonies were buildings to house twenty or thirty patients, while cottages were provided for families. The inmates were allowed to marry, but if there were children they were removed at birth, brought up away from their parents and breast-fed by paid nurses from adjacent villages.

There is nearly always difficulty in enforcing the undertakings of those still infective let out on parole. The plan has been tried in the Unfederated Malay States, notably Kelantan. Here there is a small Leper Hospital outside Tumpat and non-Kelantan lepers are sent to Pulau Jerejak in the Straits Settlements or to Sungei Buloh in the Federated Malay States. Local, Kelantese, lepers who are averse to going to the hospital undertake to keep isolated and to abstain from travelling in public vehicles, from visiting licensed premises or dealing in any trade prohibited by the Leper Enactment, but there is evidence that some at least do not abide by the conditions to which they have agreed.

In Malta also it was only the non-infective patient who was allowed to remain at home and then under supervision. According to Ehlers home segregation in the Danish West Indies was permitted only on condition that the patient had separate rooms, and feeding utensils, clothes, linen, bedding and washing accommodation restricted to his use. But no healthy child under fifteen years of age was allowed to live in a house where there was a leper. It is difficult to see the reason for this, unless the native of fifteen is supposed to have reached the age of discretion and to be able to guard himself against infection. There had been no compulsory segregation prior to 1908 when a law was passed making notification obligatory and a colony was formed. Immigration of lepers was checked by legislation against their admission and compelling shipping companies to take them back to their port of embarkation at their (the Company's) expense.

The Leprosy Commission of the Académie de Médecine agreed with home segregation only under conditions such as those detailed above—separate rooms and separate utensils and linen.

As regards the British West Indian Islands leprosy incidence has fallen when segregation is carried out, as in Jamaica, where leprosy has become almost a 'rare disease', in 1933 there were only twenty-two fresh admissions. In British Guiana also, though the Leper Hospital can accommodate 479 patients, in 1933

only 303 attended altogether, and of these fifty-nine were re-admissions

Trinidad affords a contrast Prior to 1915 there were no compulsory powers to segregate and in the latter half of the nineteenth century the incidence had steadily increased from 0.8 to 1.5 per mille The first result of introducing the compulsory system was overcrowding of the accommodation at the asylum and many absconded Sir Leonard Rogers states in his work (with E. Muir) in 1923 that an island settlement was being provided capable of housing all the lepers in the British West India Islands and

if funds are forthcoming to carry this admirable project to completion, with adequate medical staff and efficient treatment, leprosy might be practically eliminated from this important group of British Colonies within two or three decades, and an object lesson provided to the world at large

To the Chacachacare settlement, Trinidad, admissions average about seventy annually, but some 14 per cent of the inmates are free from active disease and not a few discharged lepers are re-admitted because they cannot support themselves and, owing to economic conditions, their families cannot afford to keep and look after them

Rogers and Muir have summed up the general opinion of those who have had most experience in leprosy control and they conclude that, in most places, compulsory segregation is not practicable and is often harmful In China and parts of Africa, for example, the numbers are too great for segregation to be a feasible proposition, if any attempts are made to enforce it, the patients and their friends will conceal them and the disease is spread widely in secret There is no doubt that, as in other matters of administration, a vacillating policy is worse than useless In French Guiana in the sixty-eight years, 1823-91, there have been a score of different administrative decisions, in Havana "the segregation question assumed the status of a political football," and before an election the unpopular segregation would be relaxed In Hawaii the question of segregation was a difficult problem Few lepers would apply voluntarily, many would hide and would be aided in their concealment by relatives till they reached an advanced stage and became a burden, moreover, the people had no fear of contagion

Again, in Brazil, Texas and elsewhere, in the Southern United States segregation, except as a voluntary measure, met with serious political opposition

Hansen and Looft have summed up the position in the following words

We find everywhere that decrease of the disease depends on the numbers isolated in the asylums. Where the isolation was insufficient or absent there was no decrease, but the numbers either increased or remained stationary, where, on the contrary, isolation was thorough, decrease was invariable.

Nodular cases constitute a far more serious menace than the nervous, maculo-anæsthetic type, and where segregation is not in force increase runs proportionately with the percentage of the former roaming free in a district.

The benefit resulting from humane methods of segregation and isolation is well exemplified by the history of leprosy in Norway. This was becoming evident in the eighteen-seventies, in 1885 segregation was enforced more strictly and there ensued a steady decline. There is hardly any need to adduce concrete instances to illustrate the foregoing general remarks, but one or two may be mentioned. Probably segregation has been carried out more thoroughly in Australia than in any of the British possessions and there the disease is well under control. The problem in South Africa is a more difficult one because of the mixed population. At the beginning of the nineteenth century leprosy was known to be prevalent in Cape Colony, and during the next ninety to a hundred years segregation was half-heartedly carried out or left in abeyance and the disease increased. Greatly improved results have followed stricter measures in the present century. In the United States, as mentioned above, politics interfered to a degree with enforcement of segregation, until in 1916 the Committee of Public Health and National Quarantine took up the question and reported in favour of compulsory segregation of lepers.

In the Philippines we have an example of the benefit from segregation judiciously, tactfully and humanely applied. The American sanitary authorities, under Dr Victor G. Heiser, in 1906 founded the Culion Leper Settlement and by 1918 the mortality from leprosy had dropped to 62 per cent of its former rate. In Fiji segregation has been carried out at Makongai since 1911, there are five leper villages, one for each race, under headmen, themselves lepers. Others are allowed to stay in their homes provided a medical man certifies that isolation there is adequate. As in Madagascar, those bacterially negative—but in this instance for two years—may be discharged, but are inspected quarterly and should they relapse they return to segregation. The sexes are

kept apart, but their lot is lightened by provision of agricultural work and amusements of various kinds

In the Malay States, which cannot be dealt with separately, much improvement has followed the passing of the Leprosy Prevention Ordinance of 1893

At the All-India Leper Conference held in Calcutta in 1920 Rogers advocated measures which have since been fairly generally adopted in that country, namely, the establishment of large colonies away from the towns, with ample ground for cultivation and adequate medical staff. Most of the inmates of Indian asylums, however, are in advanced stages of the disease, mutilated, helpless, but with little infectivity—'burnt-out' cases

There are controlling laws and regulations in British African possessions, but the high rates of infection make it difficult to carry them into execution. Tanganyika has leper villages where the inhabitants by cultivation of foodstuffs are almost, if not entirely, self-supporting, and many lepers come voluntarily asking to be admitted. Another advance in some colonies is the outpatient leper clinic at hospitals, for patients seen in an earlier stage when their affliction is amenable to treatment, also opportunity is taken to separate dangerous cases and to give warning and advice to others

Clearly it is one thing to make laws, quite another to have them carried out. In so many countries abroad there are laws, decrees, regulations referring to the prophylaxis and control of leprosy, which on paper are almost ideal, but, alas, only too often they are merely rules *pour épater*, not for execution. Not infrequently one notes that there is, or is to be, rigid separation of the sexes but in the vital statistics births in the asylum continue to be registered. Naturally if a law is too drastic it defeats its own ends, for, in leprosy, it will lead, as stated more than once already, to concealment and occult spread of infection

A few more words are called for as regards Leper Institutions and in particular Leper Colonies, as the most modern and, so far as can be seen at present, the most successful form of prophylaxis. It goes almost without saying that they should be run as humanely as possible, with as little interference with personal liberty as will attain the end in view, voluntary submission without compulsion will thus be gained. Hence a leper institution should not be in a town, where it will acquire the character of a prison, but as a colony away from the town, in the open, with plenty of space, land for cultivation and communal life, with occupation and

amusements and, of course, up-to-date supervision and treatment. To this end there should be a hospital for those in an advanced stage and the mutilated, a section set apart for early cases in a stage amenable to treatment, a separate house for the healthy children of lepers, and such facilities as are feasible for agricultural and other industrial occupation. Such a colony will become to a great degree self-supporting, the workers may make a little by selling their produce to the colony, and thereby have a further incentive to industry and to forget their sad lot.

The above is the main line of procedure in several of the British colonies which need not be specifically mentioned. Further, at the out-patient departments of hospitals, at Calcutta Medical College, for example, but there are several others in the colonies, a look-out is kept for cases, so that, according to the stage of their disease, appropriate measures can be taken for their treatment and disposal.

Though not a mode of prevention which recommends itself to the humane ideas of leprologists to-day, it may be of historical interest to record a recent return to the old method of disposal of lepers by murder, as if the wheel had turned full circle. The method which was put in action in parts of China in 1937, if somewhat drastic, is certainly most radical and immediately successful. Three times during the first half of the year batches of lepers were collected together and shot. To quote the words of the record, "It is believed that such a method, if persisted in, will eradicate the disease altogether." As death is certain it is considered better for the patient and for society that the life of the former should be ended painlessly and, in some parts of China, euthanasia is synonymous with the action of a firing-squad. The following is the account of Dr J L Maxwell, Secretary of the Council on Medical Missions.

As the sun was rising on Easter Sunday morning from fifty to sixty Christian leper men and women were murdered by soldiers at the leper settlement of the Yeung-kong mission hospital in Southern Kwantung.

For over twenty years this settlement has ministered to the needs of some of the lepers in this region under the able supervision of the doctors of the Yeung-kong mission hospital. During this period the inmates have received regular medical treatment, many of them had greatly improved and a number had become quiescent and non-infective cases.

Some financial help had been given by the local Chinese community.

Such funds have not, however, been sufficient to meet completely their needs and has [*sic*] been supplemented by begging.

Some three weeks ago a senior officer of the soldiers in the neighbourhood took up a very hostile attitude towards the poor people and threatened to shoot any lepers that were seen about. He sent a message to this effect to the local authorities.

On the Wednesday before the massacre, however, the military notified the lepers that all lepers in the settlement would receive 10 cents a day. It is evident now that this was done to try and get as many as possible into the settlement with a view to killing them off. Each inmate had to sign his name when receiving his 10 cents. This continued on Thursday, Friday and Saturday.

On Sunday morning early the inmates were called together to receive their money but, as soon as they had assembled, soldiers rushed in, bound them individually, dragged them out of the settlement and shot every one. Two trenches were dug and the bodies of the men thrown into one and those of the women into another, lime thrown over them and the trenches filled up. Of those murdered between fifteen and twenty were women and the rest men.

This, it is thought, will lead to an increase of leprosy in the area affected, because for years every leper will be driven into hiding and none will dare to come out for treatment.

4 CAUSATION

For many hundreds of years, in fact until the last quarter of the nineteenth century, people were not worried so much about the actual *causa causans* of leprosy as with control measures to prevent those associating with lepers from contracting the disease. Those who came most in contact with it do not seem to have concerned themselves with ætiology, as in the case of malaria, yellow fever, plague or cholera, but with prevention considered apart from actual causation. In other words, subsidiary or auxiliary factors capable of assisting and promoting extension were given first place and the primary factor—the cause—was relegated not even to the second place, it was lost sight of altogether.

At one time *climate* was held to be the chief, if not the sole cause, but a little rational consideration served to exclude such a theory, for the disease was found under all varieties of climate and climatic conditions—of soil, vegetation, temperature and rainfall. Thus, 150 years ago it was known to be present in countries differing completely in climate—in England, India, China and Iceland. Also under all kinds of physical conditions—in plains, valleys and tablelands—though in countries where it occurred it was noticed to be more intense in, and in early days confined to, sea-coast towns, as in Norway, Spain, Portugal, the Adriatic, Ceylon, China, Brazil, the West Indies. The explana-

tion was, of course, that these were the ports of entry for immigrants. Moreover, there were exceptions such as Sicily, Madeira, Abyssinia where it was more prevalent in the interior.

Explanation next was sought in *general insanitation*, poverty, overcrowding, exposure, malnutrition, but cases were observed frequently among the well-to-do, and as more investigation was carried out it was noticed that the disease was disappearing in districts where the poverty, insanitation and density of population were as bad as ever. We may refer in this regard to the insanitary conditions of the habitations in Iceland (pp 581-3), undoubtedly fostering spread, and increasing prevalence, but not causing the disease.

Contagion and Communicability were recognized on clinical grounds long ago, in the Middle Ages and even in biblical times, and it is strange to us now to see men appointed as specialists by the Royal College of Physicians to investigate the disease as recently as 1865 and the Goulstonian Lecturer of 1870 expressing their considered opinion that leprosy was not contagious. That the opposite of this was the general belief is evidenced by the establishing of leper-houses (the first in England in the seventh century). Though this was the general belief there was little real evidence in support of it and the long incubation period would add to the difficulty. Brunelli has aptly expressed it *L'opinione era contagiosa, e non la malattia*. As time went on the idea of the contagiousness of leprosy began to lose ground—we have seen how lepers were allowed to leave their asylums and mix with healthy people and beg—until discovery of the bacillus by Hansen in 1874 led to its revival, and contagion was then thought to arise either directly or indirectly by spores in articles which had been handled or worn by lepers.

The weight of evidence seemed to be against contraction by contact, because, with every opportunity, it spread so little, or rather so slowly when individual cases were studied, lepers mixed with the public and healthy paupers lived with lepers for months, it might be for years, without showing signs of having become infected. Again, many instances were noted where only one in a family was a leper, and nurses and doctors attending lepers escaped infection. Bargigli's barbarous experiment would be quoted in which he inoculated leper pus into children between six and eight years old, with negative results. All these noted observations failed to take into account the long incubation

period, on the other hand had others become infected community of source would not be excluded, as they were living in an endemic area. Lastly, in parts of China, in India, in Iceland decrease was observed without enforcement of segregation, and opponents of the idea would adduce that in cases where contagion seemed to play a part, as in overcrowded districts, poor diet, malnutrition and general insanitary modes of living could not be excluded.

There are several difficulties in tracing the source of infection the incubation period is variable but usually long, months to years, the average being a little under five years, also symptoms develop slowly, especially in the maculo-anæsthetic type, and, thirdly, there is always a tendency on the part of the patient and of his relatives to conceal its presence, especially in the earlier stages. In Norway when the disease was known to prevail only about one in five was diagnosed within three years of the first appearance of symptoms (Rogers and Murr). Of more value than much theoretical negative or doubtful evidence are the few known instances of group infections which have been traced and authenticated, such as the Natal outbreak of 1843 started by two natives coming from the Cape, the Louisiana outbreak from 1866 started by Mrs Ourblanc, the Cape Breton outbreak of 1881, the Memel outbreak originating from Russian women lepers coming as domestic servants, cases in Colombia where a merchant became infected by his negro slaves and others from him, lastly, the Rodriguez Island outbreak of 1880 onwards already referred to.

A few words on these will be of interest. Leprosy is thought to have been introduced into Natal (see p 585) by two natives who in 1840 had migrated to the Cape where they lived for three years with a leper woman. Two years after their return to Natal they developed the disease. They married healthy Natal women, but they infected the kraal and tribe after tribe became infected. By 1886 more than a hundred cases had been traced to these returning natives and in less than another decade a further 132 cases had developed.

As regards Louisiana, after an absence of leprosy for eighty years a case was observed in 1886, a Frenchwoman who died of the disease four years later. In the course of the next two years her daughter and three out of four sons developed it and three years later a nephew living at a distance contracted it. He was accustomed to visit his cousins. In the meanwhile a young girl who had nursed the mother showed symptoms, in 1873. Others developed it later who had had intercourse with members of this family, nursing, or visiting, or sleeping with them.

The Cape Breton outbreak started in a woman, Betsy McCarthy, living on Prince Edward Island. She developed leprosy at the age of fifty-two, and five of her children, four boys and a girl, contracted the infection and died of it. The daughter's husband also fell a victim six years later, as did two of their children. A son-in-law of Betsy McCarthy at one time used to sleep with one of the infected sons and contracted the disease. There were no other cases except this family focus known in Prince Edward Island.

All cases of leprosy are not equally contagious and on the other hand all contacts are not equally susceptible. Thus, nodular forms with ulceration and discharges are far more dangerous than cases of the maculo-anæsthetic type. In the Pacific Islands, Hawaii, the Loyalty Islands, for example, nodular forms predominate and the spread is rapid and as regards the contacts children are more susceptible than adults, from five years onwards with increasing susceptibility through adolescence, then decreasing after thirty to forty years. Records obtained by the Indian Commission, by McCoy from Molokai and by Tonkin of Northern Nigeria and the Sudan, show that half the cases of infection occurred under twenty years of age, 67 per cent by twenty-five years and 75 per cent by thirty years. Of those under twenty years 6-8 per cent were under six years, 20 per cent under ten, and 35-40 per cent were fifteen years of age or less. Tonkin showed that in Nigeria and the Sudan 39 per cent were less than ten years old when infected and this proportion increased to 73 per cent by twenty years and to 85 per cent by thirty years. In the West Indies Munro of St Kitts found 68 per cent up to twenty years and 84.7 per cent up to thirty years. Increase has been noted at school age, as, for example, in Hawaii, where the schools are held responsible for much of the spread.

Duration of exposure and degree of contiguity naturally are important factors, indeed they are the chief reasons for separating children born of leper parents as soon as possible after birth. Though many cases of conjugal leprosy have been recorded this is less common than a casual observer would expect, due, it is thought, to marriage taking place at an age when susceptibility is lessening, thirty years and upwards.

The question of communicability is of historical interest because of the wavering decisions which were promulgated in the second half of the nineteenth century and particularly in the seventh and eighth decades. In 1862 the Royal College of

Physicians, at the request of the Secretary of State for the Colonies, appointed a Committee to study the question, and the value of their deliberations may be gauged by the fact that they approached the problem in a way which would naturally preclude bias, for none of the members had had any experience with the disease worth mentioning. Gavin Milroy did pay a short visit to the West Indies, but the value of his opinion may be formed from his conclusion that yaws was not a communicable disease either. On the strength of the report issued by the College concluding that "Leprosy is essentially a constitutional disorder, indicative of a cachexia, or depraved condition of the general system" [a return to Danielssen's "blood dyscrasia" of 1848], and that leprosy was "not contagious or communicable to healthy persons by contact with the diseased," the Colonial Secretary issued orders that the laws should be repealed which affected the personal liberty of lepers. This, as would be expected, was succeeded by a definite increase in prevalence.

The rise in incidence following closure of leper hospitals and removal of restrictions stimulated further investigation and evidence began to accumulate in favour of communicability, notably by Drogant-Landr  who published a book, *De la Contagion seule Cause de la Propagation de L pre*, in 1869, from observations in Guiana, the conclusions of the British Guiana Leprosy Commission of 1875, Munro's article in the *Edinburgh Medical Journal* of 1877 among others, all pointed to the same end. Liveing, in his Goulstonian Lectures in 1873, cautiously concludes that leprosy was not contagious in the ordinary sense of the word, but was "propagated by the imbibition of the excretions of those affected." In the course of the ensuing fifteen years several writers published articles stressing the communicability of leprosy, such as Brousse of Trinidad in 1879, Hillis of British Guiana in 1881, J. C. White in America in 1882, Leloir, Brocq and Vidal in 1885, and Besnier in 1887. The Indian Leprosy Commission of 1889 published conclusions the opposite of this. This Commission included two Indian medical officers, two medical men from England with no previous experience of leprosy, and Dr. Beavan Rake of Trinidad, a man with pronounced anti-contagionist views, nominated by the Royal College of Physicians. The last-named made the board clear by ruling out all cases in an endemic area as being of no evidential value. The Commission adopted his view that leprosy originated *de novo*, a view, however, which the Executive Committee of the National Leprosy Fund, which had appointed the Commission, repudiated.

Every Leprosy Conference of importance since has supported with practical unanimity the view that the disease is communicable, although the precise manner in which the healthy becomes infected is still unsettled. The position was summed up towards the end of last century (1893) accurately, if somewhat vaguely, by the Leprosy Commission thus

An endemic area would be one where (a) the virus in some form or other is present and where also (b) such conditions exist as are calculated to receive a special predisposing influence on the population, thus enabling the parasite not only to enter the body, but also to grow and thrive in the same

It would hardly seem to need a Commission to state, nineteen years after Hansen's discovery of the bacillus, that an endemic area was one where the seed was present and the soil ready to receive it. It did service, however, in relegating poverty, famine, insanitation, overcrowding and heredity, to their proper place as auxiliaries

It has been suggested that leprosy might be conveyed by the former custom of inoculating for smallpox, and theoretically in countries where leprosy was common, China for example, this would appear to be a real danger. Investigation shows, however, that such inoculation was introduced into China in the eleventh century when smallpox was rife among adults. They inoculated children only and it is noteworthy that the Chinese, astute observers though they are, have never attributed leprosy to vaccination.

That heredity was the only mode of conveyance beyond question was for long held. "There is almost complete unanimity on this point among observers of all times," writes Hirsch, but whether the disease itself is inherited or merely the predisposition is not decided. Hansen stated the position in these words: "If the disease be a contagious one it may communicate itself by its virus to the foetus in the womb, but then it is not hereditary, if it be non-contagious, it cannot be conveyed to the foetus in any way whatsoever," surely a strange method of arguing. Others have suggested a latency of many years or a "congenital morbid diathesis." Hansen himself investigated the descendants of 160 Norwegian lepers who emigrated to the United States, and found that all the offspring had remained free to the third generation. He, therefore, held that hereditary transmission played an almost inappreciable part. On the other hand the disease arises at times in those without any leprous history or inheritance, as in Europeans leaving home and acquiring the disease in the tropics.

In China, Japan, and in Northern Nigeria the hereditary idea has been a matter of general belief for centuries, but even there it is admitted that the taint may delay its appearance for years, perhaps till puberty. It is important to remember that the evidence adduced in support of heredity is largely, almost entirely, based on inquiries made in geographical areas where the disease has prevailed for generations. J. C. White put the issue plainly in 1882 when he stated "The theory of heredity will not hold good in any instance without the absolute demonstration that inoculation has been impossible."

Diet as a cause, in particular *Fish*, is a theory which has had many, and among them notable, adherents. In the eighteenth century the 'Fish theory' had a wide vogue. In reality there were three fish theories. First, that leprosy arose from excessive use of fish as food, second, that it was a form of food-poisoning due to eating fish which had been allowed to become putrid, thirdly, that it was due to transference to man of a leprosy-like disease of fish.

In Devon and Cornwall we find recorded covenants stipulating that "no apprentice or servant shall be obliged to dine on salmon more than once or twice a week" [many would consider themselves in luck if they had it once a week now]. Others came to the same conclusion that leprosy and fish-eating were intimately connected ætiologically, by a 'process of exclusion'—not a very weighty reason for the faith that was in them, for if the suggested causes had been considered in a different order, this would be excluded also, or in place of another. Certain it is that leprosy occurs where no fish is taken, at all events is not taken to excess nor in a state of decomposition, in parts of Africa where leprosy is common the natives will not touch fish, regarding them as snakes. On the other hand the disease has disappeared apparently spontaneously in places where the diet has remained unchanged.

It is true that as vegetable produce came more and more into the common dietary and more fresh animal food replaced the badly preserved and tainted meat and fish leprosy became less common. The dietetic origin of leprosy was held by Creighton who compared it with pellagra—a disease thought in his day to be due solely to damaged maize—saying "in pellagra we find the key to the ancient problem of leprosy. The two diseases are closely allied and may be reasonably suspected of having analogous causes." Also, in Newman's *Prize Essay on Leprosy*, we read as

regards Iceland "Since fishing has declined among the inhabitants of the islands of Ferro and the inhabitants have cultivated corn and live upon other food instead of whale flesh and bacon, the elephantiasis has ceased among them"—another example of the *post ergo propter* fallacy

Again, in New Zealand, the early colonists found leprosy prevalent among the Maories who were living on very restricted supplies of food and being near the sea-shore their main food was fish. The British introduced corn, sheep and cattle, the Maories took to farming and spread more inland, abandoned fish and replaced it by mutton and Indian corn. "The result has been," writes Jonathan Hutchinson, the staunchest upholder of the fish theory and who called leprosy "fish-eaters' gout," "that, without any attempt at isolation, leprosy has within quite a short period almost wholly disappeared." Dr W H Ross, of Robben Island, was of the opinion, and he adduced the experience of lepers there in his support, that fish diet does cause an exacerbation of leprosy. But in many countries with a littoral, the diet of the inhabitants is poor and consists largely of fish, yet there may be no leprosy, and in others there is leprosy although fish enters but sparsely into the dietary.

Jonathan Hutchinson was far too sound a reasoner to base his theory on the mere concomitance of fish-eating and leprosy. Other points which he adduced, in 1901-03, were (i) that the bacillus itself may infect fish in certain conditions of partial decomposition, or that some element may be generated in connection with such fish which may excite the bacillus, when already present, to fresh development [this alternative is very hypothetical] (ii) In leprous countries the disease is most rife among the coast-dwellers (iii) That its incidence is greater among Roman Catholics than among those who do not eat fish as part of their religious observances (iv) That strict vegetarians, such as the Jains and the high-caste Brahmans, are almost free from leprosy. Hutchinson contended that this theory explains several obscure epidemiological points such as the antiquity of the disease, its widespread prevalence, its local distribution in a country, its prevalence in Roman Catholic communities, its disappearance with the advance of civilization and the absence of the disease in mid-Russia. He disbelieved strongly in the idea of contagion and therefore denounces asylums as cruel and unjust, "the result of overweening confidence in scientific dogma."

Fish-eating is almost universal and it is a truism to say that "all lepers are consumers of fish but not all consumers of fish are

lepers," though prolonged use of fish may lower the vitamin content of the diet and so predispose to infection

The view that leprosy might be due to a *specific virus* did not take its origin from Hansen's discovery of his bacillus. More than a hundred years before, namely in 1769, Schilling had written "Neque tamen negaverim peculiarem esse materiam et quāsi virus quoddam, sine quo vera lepra non producat" But we hear no more of this till 1874 when Hansen stated that he had found "organic elements in the morbid products which are perhaps the proper virus of leprosy"—Hansen was a cautious man—rod-like bodies, and in older morbid products brownish cells of larger size containing zooglōa masses and aggregated bacilli. Among others, Neisser confirmed this and found these rods in practically all leprosy lesions, skin, mouth, larynx, liver, spleen, glands, nerves, etc. He held that the evidence of its being causative was satisfactory, though, in the absence of cultivation, the final scientific proof was lacking. In spite of this no one of any repute has since this time doubted that Hansen's discovery was the true solution and his bacillus the immediate cause of the disease. Kaposi should be mentioned as an exception in that, though he was in general agreement, he maintained a reservation that there were cases in which the bacillus could not be found.

The only questions debated have been those concerning the modes of introduction into the body, whether by the unbroken skin—contagion, by a broken surface—inoculation, by foetal transmission—heredity, or by air or food—communication (as interpreted at the end of the nineteenth century)

We now come to an interesting stage in the history of leprosy, namely, the attempts at cultivation of Hansen's bacillus—now known as *Mycobacterium leprae*. Many have claimed to have succeeded, but other bacteriologists have steadfastly refused to recognize these claims—the results have been very variable—and we may state that up to the present there is no proof that the cultures obtained were those of the lepra bacillus. There have been at least a dozen of these and we will speak of them briefly in the chronological order of their being reported. Hansen's bacilli, as seen in the tissues, vary in size from 1 to 8 microns in length, are straight or slightly curved, occur in clumps or bundles, are non-sporing, Gram-positive and acid-fast.

In 1899 Carrasquilla claimed to have cultivated the organism on sloped solidified human serum and beef bouillon, and that he

had obtained pure subcultures in series from serum to serum and bouillon to bouillon. He described the organism as of two forms one long and slender, the other short and elliptical. He noted that it resisted decolorization by 30 per cent nitric acid, that filtrates from cultures injected into horses produced the same reaction as serum from lepers and that the serum of horses after injection of culture filtrates produced the same reaction in lepers as the serum from horses injected with serum of lepers' blood.

The same year Max Teich claimed to have cultivated it on potato peptone nutrient agar. His organism was acid- and alcohol-fast, was in the forms of thin rods or thick oval bacilli and markedly pleomorphic. Similar growths were obtained by Babès, Spronck, Bordon-Uffreduzzi, and others, but experimental inoculation did not furnish confirmatory evidence of their being causative of leprosy.

In 1901 Kedrowski grew a non-acid-fast diphtheroid (though young cultures might show some degree of acid-fastness) with branching forms and he classified it as belonging to the *Actinomyces* group and believed it to be a stage in the development of Hansen's organism. Three years later Rost (see also below) stated that he had succeeded in growing the bacillus, using distillate of beef-extract. It was important that the medium should be free from NaCl. He obtained growth after 4-6 weeks at 37° C. 'Leprolin' is the fluid filtered off to which glycerin is added. If injected into lepers it caused swelling and inflammation of the local lesions and a rise in temperature [results probably due to injection of foreign protein]. Semple repeated Rost's work but failed to confirm his findings.

In 1905 also P. H. Lie of Leipzig posed a fresh problem in connection with the bacteriology of leprosy. He described anew the detailed pathology of the two types, nodular and maculo-anæsthetic, and wondered whether the bacillus might differ in virulence in the different types of disease or whether the difference might be attributable to varying resistance on the part of the patients, and he suggested once again the possible effects of climate, in a dry climate as that of eastern Norway the maculo-anæsthetic form prevailed, on the stormy and moist west the nodular was more frequent. All this was purely speculative but deserves passing mention in view of the different characters of organisms grown by different workers from similar sources—lepromata and lepromatous lesions. In 1905 Emile-Weil obtained growth of Gram-positive, acid-fast organisms by inoculating glycerin glucose peptone agar and egg-yolk with leproma juice.

He was unable to obtain sub-cultures. The following year (1906) Deycke and Reschad grew a streptothrix from leprous tissue in broth and they found that injection of their culture into the patient from whom they had obtained their original material was followed by [they said "produced "] evident improvement in symptoms [see below, Nastin in treatment]

In 1909 Clegg obtained a weakly acid-fast chromogenic bacterium by growing the leproma tissue with amoeba and cholera vibrios. By heating the mixture to 60° C for half an hour he killed off the two latter leaving a pure culture of his acid-fast bacillus. In morphology and cultural characteristics it resembled the saprophytic acid-fast bacilli and inoculation in guinea-pigs produced similar lesions to those of the latter. In 1910 C. W. Duval grew a non-chromogenic acid-fast organism on agar or banana medium with 1 per cent tryptophane. When inoculated into the usually employed small laboratory animals no effect was produced but in Japanese dancing mice miliary tubercles were formed which contained acid-fast bacilli, mostly intracellular.

In 1911 there were several reports of successful cultivation and in this year, too, T. L. Sandes, working at the Robben Island Asylum South Africa, recorded the finding of typical acid-fast bacilli in bed-bugs which had fed on leprosy patients. This was not an unexpected finding, but the importance of it was that he interpreted their presence in large numbers as indicative of multiplication in these insects. He observed them up to sixteen days. This also opened up new ideas on the possible modes of transmission. E. C. Long in Basutoland had independently made the same discovery the same year.

Duval reported further on cultures obtained by Clegg in 1909 and described the growth on alkaline human- or rabbit-blood agar and glycerinated serum agar. With this he infected white mice, Japanese dancing mice and monkeys by subcutaneous inoculation and by application to the nasal mucosa.

E. R. Rost and T. S. B. Williams in a Scientific Memoir on cultivation of the bacillus reported in the *Irdjar Medical Gazette* isolation of a pleomorphic streptothrix, or a diphtheroid organism becoming an acid-fast streptothrix like that of Rost and Deycke, and stated that they found it also in the reactions resulting from the use of Isprolin (v.s.) prepared from their cultures. Rost reported success from its use as a vaccine in twelve cases of leprosy; five were completely cured and seven remarkably improved—a good instance of the importance of employing a remedy while it is new.

It is not quite clear from the literature whether the organism

or organisms referred to are the same as the acid-fast chromogenic and pleomorphic bacillus which Rost grew on a medium composed of milk broth and "volatile alkaloids from rotten fish" They reported the development of two organisms, one like Rost's (chromogenic acid-fast) and the other a non-acid-fast streptothrix.

The following year H Bayon cultivated from two leprosy patients in London a pleomorphic organism closely like that described by Kedrowski in 1901 (v s) and later by Deycke, Rost and others. On cultivation it yielded a non-acid-fast streptothrix, a diphtheroid, also non-acid-fast, an acid-fast filamentous growth which, on breaking down, formed acid-fast bacilli. From experimental injection in rats and mice Bayon concluded that the human leprosy bacillus existed in three stages. Duval the same year, with Wellman, made further announcement of growing organisms of three forms from the lesions, an acid-fast chromogen like that of Clegg, a non-chromogenic like Duval's and a non-acid-fast diphtheroid like that of Kedrowski. In 1912 also Currie, Clegg and Hollmann grew an acid-fast chromogen which culturally did not differ from acid-fast saprophytes. Agglutinations of it were tried with sera from leper patients, but only occasionally was the result positive.

In 1914 McCoy obtained similar cultures, but animal inoculation produced nothing resembling leprosy. At Kuala Lumpur H Fraser and W Fletcher obtained fragments of nodules excised from patients in the asylum, only half a mile from the laboratory, and found them swarming with bacilli but did not succeed in growing the organism by any of the methods noted above—Clegg's, Rost's, Williams's, Duval's or Bayon's. Further, they carried out inoculation experiments with cultures supplied to them by Kedrowski and Bayon and found that the lesions resulting might be produced also by dead bacilli and by other acid-fast organisms such as the smegma and Rabinowitsch's bacillus, in fact, they could find no evidence confirming either Kedrowski's or Bayon's organism as causative of leprosy.

Efforts were not relaxed and the zeal for growing the leprosy bacillus emulated that of the inveterate π -computers of last century. The work described above and that carried out during the ensuing fifteen years were summed up by E L Walker in 1929 (*Journal of Preventive Medicine*). He dealt with 607 lots of pathological material from 194 patients and made 2363 cultivation experiments on every type of material such as had been used for spirochaetes and protozoa as well as bacteria, and anaerobically as well as aerobically, under varying gas tensions. Most remained sterile,

others showed coccoid forms, diphtheroid rods, filamentous branching forms. These he isolated in pure culture and found they bred true and concluded that the organism cultivated from leprous material was not only pleomorphic and facultatively acid-fast, but that it had a life-cycle represented by different morphological forms. He placed it among the Actinomycetes and believed it to be a soil organism gaining entrance through wounds.

The next development of note was Shiga's work. He ground up excised lepromata with 5 per cent sulphuric acid, left it for twenty minutes in the incubator, centrifuged it thoroughly, poured off the supernatant fluid, washed the deposit and again centrifuged and inoculated glycerin potato medium with it. In a month at 37° C the inoculum seemed to have degenerated, but in two months small colonies formed, greyish-white and somewhat more moist than *Mycobacterium tuberculosis*.

There have been several attempts reported in the past seven or eight years, but only two need be specifically mentioned, namely Vaudremer's, and Soule and McKinley's. The former has recorded beneficial results from treating lepers with a vaccine prepared by cultivating fragments of nodules on an aspergillus medium and subculturing what he regards as evolutionary forms on gelatin. Soule and McKinley in 1932 incubated leproma suspensions in different media in varying partial presence of oxygen and carbon dioxide, 40 and 10 per cent respectively, and obtained sixteen subcultures in eighteen months, in each case acid-fast. By 1937 McKinley and De Leon reported having carried the cultivation through sixty generations. The most successful medium has proved to be hormone-glycerol-agar (described in the *International Journal of Leprosy*, 1937). Salle and Moser, working in the Carville Leper Settlement, United States, and using glycerin veal agar with chick embryo and the gas conditions of McKinley, have obtained acid- and non-acid-fast rods, the former most numerous in young cultures and becoming fewer as the culture aged, and more again on subculture. They thus confirm McKinley and Soule's original work.

Throughout 1936 attempts were made at the Calcutta School of Tropical Medicine to confirm the reports of successful cultivation by McKinley, Soule and Verder. Twenty-four series of experiments were carried out and a thousand tubes of different media inoculated. Half were incubated in the usual way and half under the gaseous tension recommended by McKinley and Soule. The tubes were examined periodically over several months. Of seventy tubes seeded in August and kept in a gaseous environment

of 40 per cent oxygen and 10 per cent carbon dioxide, thirty-five showed slight macroscopic and considerable microscopic evidence of colony formation and many masses of acid-fast bacilli were seen in smears. Of another seventy under ordinary atmospheric conditions fourteen showed similar but less evident growth. Subcultures were being attempted, but it was acknowledged that multiplication of bacilli had so far not been proved, nor had the organism been demonstrated to be *Myco lepræ*.

In minced chick tissue medium bacilli persisted for a long time, but there was no multiplication. Salle held that they multiplied in alternating acid-fast and non-acid-fast forms, but this was shown to be erroneous. The bacilli (unless contaminants are present) remain acid-fast and the non-acid-fast contaminants do not become acid-fast in fresh media.

Success, however, at length seems to be in sight. In 1936 S. E. B. Balfour-Jones, working in the Medical Research Council's laboratories at Mill Hill, was able to transmit the bacillus of rat leprosy to Syrian hamsters. Professor S. Adler of the Hebrew University, Jerusalem, on returning from a visit to England, proceeded to carry out the same with human leprosy and the preliminary results, which are all that are known at present, indicate that the bacillus of human leprosy will readily infect the hamster and produce in it a characteristic disease. He finds that subcutaneous implantation of a fragment of leprous tissue is followed by intense multiplication of the organisms and they are found at a distance from the point of inoculation, such as the liver and testis. Burnet confirmed this by experimental production of the disease in one of these hamsters inoculated with a piece of leprous tissue between the skin and muscle layers. When the animal was killed 220 days later it showed signs of progressive disease, the lymphatic glands, spleen, liver and kidneys having been invaded. Professor Adler is now engaged on further work as to the longevity of the bacillus outside the body and the effects of physical agents upon it, the results of inoculation by the different routes, the behaviour of the organism in the hamster as compared with that of rat leprosy and so forth.

We may here interpose a few words on the subject of Rat Leprosy, which was first reported thirty-five years ago and has been studied with considerable minuteness because of its affinities (or apparent affinities) with human leprosy and difficulties and disappointments associated for so many years with study of the latter and the hopes that discoveries in the one might throw light upon problems connected with the other.

The condition was first observed incidentally in the course of examining rats for plague and was seen by Stéfansky in Odessa and by G. Dean in London independently in 1903, in *R. norvegicus*, or as it was then called *Mus decumanus*, and the associated organism was known as Stéfansky's bacillus, now by the longer but more descriptive name of *Mycobacterium leprae murum*. Soon it was found to be very widespread and was reported in Berlin rats by Rabinowitsch (1903), in Australia by Tidswell (1904) and Bull (1907), in Kenya by De Smidt, in America by Walker, McCoy and Wherry, and in Japan by Honda and others (all in 1908), in France by Marchoux and Sorel, and in New Caledonia by Lebœuf (1912), in Porto Rico by Ridlon, in Korea by Ishiwara and in Brazil by Azevedo (1913) and elsewhere. It was found further that other rodents also were attacked, such as *R. alexandrinus*, *R. diardui* and *concolor*, and that adult rats showed a higher incidence than young, in a proportion of about four to one.

Two types occurred—a glandular in which one or more groups of glands might be involved—enlarged, firm, with foci of softening—and the musculo-cutaneous in which there were whitish skin areas, denudation of hair, cachexia and small nodules which might ulcerate. Bacilli were found in all the lesions and also in the nasal mucosa, but the primary portal of entry seemed to be the skin in most cases. Transmission was brought about by contact, the evidence for insect transmission was not convincing, and if it took place by food or cannibalism, this seemed to be relatively unimportant. Experimentally, transmission was easily procured by inoculation—intradermal, subcutaneous, intravenous, intraperitoneal, intraocular—but the resulting lesions were more visceral involvement than in the natural disease.

The bacillus was 3–5 microns in length, Gram-positive, acid-fast and alcohol-fast, even more so than Hansen's organism, it might show granular staining. The individual bacilli were not so markedly grouped in bundles as are Hansen's, nor do they form globi.

Until 1936 attempts at culture had not been much more successful than with Hansen's organism and the results have been equally varied. Whereas in lesions the bacilli present a constant morphology, multiply slowly and are always acid-fast, in cultures they are pleomorphic and not acid-fast, at all events not constantly so. Explanations put forward for this, as for the results with the human bacillus, are that when the medium is inoculated large numbers are used and many persist without actual multiplication, or that the non-acid-fast diphtheroids and the rest are contam-

nants of the inoculum or the medium, or that saprophytic organisms when injected are capable of producing lepra-like lesions

The conclusion has been reached that the human and rodent organisms, though allied, are not identical, they are immunologically distinct, and it has been suggested that the origin of both may have been a saprophytic acid-fast organism, possibly a soil organism, from which strains have developed, one adapted to rats and one to man, and others for other animals which are subject to infection such as fowl, cattle, sheep, buffaloes, opossum. If there is anything in this theory comparative studies may prove of great value in elucidating some of the obscure problems of human leprosy.

The most recent development of all is probably the application of modern bacteriology to establish the antigenic relationships of allied organisms.

The antigenic relationships of sixteen strains of mycobacteria isolated from leprosy, and of this group of organisms and eleven other strains of acid-fast bacteria, have been determined by means of the precipitin reaction, using purified specific proteins and sera of rabbits immunized against these proteins. The organisms employed all grew readily on Long's synthetic medium, which was used for all cultures, obviously, strains not growing on artificial media could not be included. With but few exceptions the antisera tested gave the highest precipitin titres with their homologous antigens. Thirteen of the sixteen leprosy strains gave strong precipitin reactions with one another. In view of this it is considered justifiable to place them in one large, antigenically related group. Of the three remaining strains, those of Duval (non-chromogenic) and Walker (chromogenic) failed to cross-react with the large group and may therefore be considered as antigenically unrelated. The one remaining strain, Levy-Kedrowsky, while it failed to give definite cross-reactions with all members of the large lepra group, did react with two of them, the Ota-Sako and Karlinski strains, and therefore has an antigenic relationship with the group.

Two points remain for consideration in this section, dealing with ætiology—first, how do the bacilli escape from a leper? and secondly, how do the healthy contract the infection? There is little need for more than passing mention of the former, the bacilli pass in large numbers from breaking down lepromata, by lesions of the skin, ulcers, and so forth (but it is to be noted that the so-called 'trophic ulcer' does not exude the bacilli), also from the nasal mucosa of 30 to 90 per cent of lepers according to various authors. Rogers in Calcutta found them in 37 per cent only of nodular cases and in one-tenth of this (3.8 per cent) of maculo-anæsthetic cases. Again, they are thrown off in coughing, sneezing, and perhaps even speaking, if ulcerated leprous tubercles

are present in the throat, and finally the milk of female lepers may contain the bacilli and, of course, swallowed organisms may pass with the fæces

As to the conditions under which leprosy is most often contracted there has been considerable controversy and the point cannot be regarded as settled yet Rogers analysed 700 cases and these revealed that, in percentages, 39.8 had lived in close contact sharing house, room or even bed, 19.8 had attended lepers, a like proportion, 19.4, had associated as playmates, and 18.2 were conjugal in origin

Vaccination has been accused (this has been referred to above, p. 622), but this would be possible only where direct arm-to-arm vaccination was carried out, and that from a case with cutaneous lesions. In the middle of the nineteenth century cases did undoubtedly so arise when vaccination was carelessly performed, by laymen. We must remember in this connection, as Rogers and Mur point out, that ordinary vaccination may in a leprosy subject cause rise of temperature—perhaps a true leprosy reaction—with local swelling persisting for as long as three weeks and perhaps ulceration and inflammation of old nodules, new ones appearing about the twelfth day and then subsiding. Some of those reported from Hawaii may have belonged to this group, the subjects being lepers in an early stage reacting thus, and not actual infection by vaccination

Inoculation by way of wounds and the possible conveyance by the agency of insects, by bite or by mechanical transference, have been referred to already. Attempts at inoculation by injecting leprosy material have usually (? always) failed, perhaps because the subjects were adults beyond the age of great susceptibility, but this was not the case with the experiments of Bargighi noted above (p. 618). The disease has been recorded as developing in a man whose duty it was to rub lepers with ointment, and in a nurse working in a leper asylum who pricked her finger with a needle. Instances are also on record of doctors subsequent to performing operations on lepers acquiring the infection

The question of insect transmission has been a vexed one for many years. The possibilities are threefold. (i) Direct transmission mechanically as by non-bloodsucking flies, like the transference of yaws spirochaetes to an open wound, (ii) By some burrowing insect, such as the itch-mite, or (iii) By the bite of a blood-sucking insect or by inoculation of its fæces or body contents. Many have been incriminated from time to time, but, however great the likelihood, actual proof has not been forthcoming

Acarus scabiei is frequently seen in association with leprosy, in the Philippines for example, lice have been shown to harbour acid-fast bacilli in their intestine after feeding on rats with rat-leprosy, but not in those which have fed on man. Rudolph of Brazil in 1918 demonstrated the presence of the bacilli in the intestine of ticks thirteen days after they had fed on a leprosy nodule, bugs, which infest leper dwellings, have shown their presence in the intestine more often than other insects, as has been noted by F. Sandes in the Robben Island asylum and by Long in Basutoland in 1911, as stated above (p. 627). 37 per cent of fleas which have bitten a nodular leprosy patient have acid-fast bacilli in their intestinal tract.

Concerning mosquitoes diametrically opposite reports have been made. Noc in 1903 stated that he found the bacilli in 50 per cent of 150 mosquitoes which had been permitted to bite lepers. Currie, seven years later, on the other hand, examined 493 and found all negative.

Lebœuf (quoted by Rogers) summed up the evidence thus: House-flies may absorb abundance of bacilli from leprosy ulcers, but these do not multiply nor do they degenerate in their intestines, and these insects may therefore play a part by depositing bacilli on numerous surfaces—the nares for example—in their excreta, or on cutaneous wounds of healthy persons in the immediate neighbourhood of lepers. The evidence of transmission by biting insects is not convincing.

5 DIAGNOSIS

We have spoken above (pp. 570-3) on the confusion in early days between leprosy and certain other diseases, mostly cutaneous, this was the result partly of clinical resemblances, partly from the want of definition as to what was implied by the term 'lepra,' for the original word which came to be translated 'leprosy' undoubtedly included other conditions than leprosy as we interpret it at the present day. In this section we deal with such modern methods of diagnosis as have historical interest.

Diagnosis in the earliest stages—the time when, if treatment is to be successful, correct diagnosis is all important—is not easy and several things militate against it. The onset is usually painless and it may in its beginning resemble minor lesions, such as that of ringworm and be ignored by the patient and his family. This ignorance is not always attributable to the patient, some medical men in practice in the tropics are woefully ignorant of leprosy, especially of its early manifestations. Again, conceal-

ment—wilful concealment—on the part of the patient and his relatives till the advanced stages when the man becomes a nuisance and a burden and treatment has no chance of success has been all too frequent, especially when repressive measures were strictly enforced

Means of diagnosis such as examination of the blood or a portion of leproma removed in life call for more than passing mention Sardjito and Sitanala have maintained that acid-fast bacilli can be demonstrated by the thick-drop method when the blood is taken from the unaffected skin of patients with nodular leprosy, and in smaller proportion nerve cases also, and they believe that this indicates their presence in the circulating blood before they invade the tissues to form lepromata The bacilli, they say, are in the capillaries, not in the tissue fluid, for the serum, if it contains them, has much fewer organisms Legendre and others have not been able to confirm this Legendre examined 237 interned lepers in this way, eighty-seven had bacilli in the nasal mucus and in blood obtained by pricking a leproma, but finger-blood (when no local lesion was present) was negative in every case

J M Gomes's 'complement fixation' test was published in Brazilian literature in 1929, though the author stated that he had been carrying it out for several years for determining the diagnosis of persons suspected of early leprosy For antigen he employed *Streptothrix leproides* of Deycke He defatted it by treating it with olive oil and acetone, growing it in glycerin broth at 37° C for twenty days The fine whitish powder was kept in a sterile flask, and for the test a 9 per cent emulsion in normal saline is made and heated to 100° C for five minutes to destroy anti-complementary bodies As a result of testing in this way 200 cases of leprosy or suspected leprosy he came to the conclusion that a positive result in contacts exhibiting no clinical signs of leprosy indicates immunity, when the positive becomes less and less to negative, clinical signs begin to appear unless the disease is in an early stage, under treatment and responding well, and cases of leprosy which give a negative reaction are usually mild In 1934 Gomes published the results of over 2000 tests including 559 lepers and 713 suspicious cases Typical nodular cases gave 96·7 per cent positive, mixed gave 95·4, maculo-anæsthetic 65·6, and nervous cases 64·8 per cent positive reactions Of the non-leprous some tuberculous patients reacted In doubtful cases the reaction was intensified by giving 2 grams of potassium iodide daily for a week

Bargehr's reaction is analogous to the tuberculin reaction and is known as the *lepromin* reaction. His antigen was originally prepared (in 1926) by sterilizing emulsions of lepromata at 120° C and keeping the product in ampoules in powder form. A little of this was applied to the scarified skin, lightly rubbed in and allowed to dry. Within a week a raised erythematous patch appeared which might remain for a month or longer. Bargehr continued to work at the subject, next preparing his 'lepromine' from localized lepromata, excising them, cutting them into small pieces, heating them with a little water in a water-bath for twenty minutes to obtain a paste, and finally adding phenol to 0.5 per cent. He uses it like tuberculin in the von Pirquet test. In 1935 Bargehr reported his further considered conclusions that those who had never come in contact with lepers reacted negatively because there had been no opportunity for antibodies to be produced, that those who had lived in contact with lepers for a long time but remained healthy developed antibodies sufficient to overcome the infection and in consequence reacted positively to the test, those with active leprosy give a negative because the development of antibodies is insufficient to cope with the infection, while those who have passed to the quiescent stage give a positive because their antibody development is adequate.

Prior to Bargehr, Mitsuda, in 1916, reported that intradermal injection of boiled emulsions of lepromata produced positive reactions in neuro-macular, but negative in nodular leprosy. Hayashi in 1933, using fresh nodules boiled in physiological saline for 30–50 minutes, ground in a mortar, 1 gramme added to 20 c.c. salt solution, filtered through gauze, heated to 60° C for an hour and with addition of phenol to make 0.5 per cent solution, carried out the test on 189 cases, injecting 0.1 c.c. intracutaneously and examining for reaction—infiltration 0.3–1.0 cm in diameter—on the eighth, sixteenth and twenty-fourth days. Of sixty-four neuro-macular cases all but two were positive, while of 125 nodular 114 were negative. In other words, speaking generally, a positive reaction occurs in normal persons resistant to leprosy and in those who are in the partially resistant neuro-macular stage. Other acid-fast bacilli, such as *Mycophiler*, and the organisms of Clegg, McCoy, Duval and Kedrowsky, react positively with all types of leprosy—another point of difference from Hansen's organism in human lepromata.

The same year (1933) there were carried out further investigations of Mitsuda's leprolin test, two forms being used. H-leprolin or emulsion of human nodules containing Hansen's bacilli, and

S-Leprolin from the spleens of rats infected with Stéfansky's organism. It was found that in the non-leprous subject H- and S-leprolins gave about the same reactions, but in dermal leprosy with many bacilli only the S-leprolin produced a reaction. In the very young, reactions to both are negative or slight, indicating a weak resistance to infection, in the nervous forms of leprosy with few bacilli the reaction to H-leprolin is increased, indicative of resistance to the infection, a strong reaction implying a favourable prognosis, and assisting treatment in that anything which changes a negative reaction with H-leprolin to a positive is likely to do good. In 1934 Dubois and Degotte made a comparison of the Bargehr and Mitsuda methods and found the latter to be the more reliable.

Rubino's test was first proposed in a publication in 1926 under the title *Una nueva reacción serológica de la lepra*, a paper read before the Dermatological Society of Montevideo. We cannot enter here into the details of the preparation of his materials, but briefly the procedure is as follows. 1 c c of the patient's serum was mixed with 1 c c of sheep's red corpuscles which had been first washed with saline and, after standing with 10 per cent formol (i.e. one-tenth of the volume) for twenty-four hours, was again washed. The mixture was placed in a thermostat at 37° C and in a positive case sedimentation took place within an hour, leaving a clear supernatant. Subsequently Castro Paulher and Errecart (1926) reported less satisfactorily on the results in their hands, but Marchoux and Caro (1928), Monacelli (1928), Peltier (1928), Markianos (1929) have carried it out in a large number of cases and have reported very favourably upon it. Marchoux and Caro found that if five parts of serum were added instead of one all their cases of leprosy gave a positive in thirty minutes, the specific substance in the serum, they found, was destroyed by a temperature of 60° C. The latest account is that of Pimentel Imbert of Porto Rico in 1936. He employed Rubino's latest method with a double series of three tubes, each containing respectively increasing dilutions of serum, fresh corpuscles with formol and non-formolized corpuscles as control. He tested the reaction in 278 sera, 47 from lepers, 17 apparently normal subjects and 214 from patients other than lepers. The reaction was positive in 70.2 per cent of all cases of leprosy, 86.2 per cent in nodular cases, 70 per cent in mixed and 62.4 per cent in nervous types. Non-leprous cases gave no positive. The Rubino reaction must not be confused with the ordinary corpuscle sedimentation

(Westergren's test) which has been studied in various morbid conditions for the past decade

Lastly, the *histamine test* of Rodriguez and Plantilla, published in the *Bulletin of the Philippine Health Service*, in 1931. This test is carried out as follows. A drop of 1 in 1000 histamine phosphate is placed on the healthy skin and another on the affected skin and a prick is made through the drops but without causing bleeding. In the healthy skin an area of 3-4 mm diameter reddens in 20 seconds, due to the vasodilator action of the histamine, flushes in 15-30 and becomes a weal in three to five minutes, with itching lasting for fifteen to thirty seconds, like a mosquito bite. On affected skin no such change is seen. In leprotic nodules in which no bacilli can be found, there is almost constantly an absence of reaction.

Chujuto the following year reported that in his view the test was not dependable in the early stages when only perivascular infiltration is present, but no neurological changes. De Sousa Campos reporting his opinion of the test in 1934 stated that he regarded it as of considerable diagnostic value in early cases where bacteriological examination has given no information. It has, however, certain limitations such as difficulty, at times, in interpreting the reaction in dark skins and in lesions themselves associated with much erythema and in dark cicatricial spots. Rivero Jimenez in 1935 reported cases showing its value in his hands and also explaining the mode of action. The erythema and weal with localized anæsthesia are indicative of intact nerve-twigs, in macular leprosy a small papule with œdema 1-2 mm in diameter appears in a minute or so, increasing to 1 cm in five minutes, but without any itching or erythematous halo. A positive reaction, i.e. erythema, papule, œdema up to 1 cm only with no itching or halo, indicates that the bacilli have invaded the nerve-endings and the macular spot tested is leprosy in origin.

6 TREATMENT

The question of prophylaxis and the control aspect of treatment has been already dealt with in sufficient detail. In the present section we confine ourselves to the history of curative treatment. There is an old saying that a disease for which there are many remedies has no cure, and the list of drugs which have from time to time been suggested and tried is a long one. It is not within our scope to evaluate these drugs, for a work on history must not be allowed to encroach too far on the clinical aspect of disease. Many persons with long acquaintance with leprosy

maintain that except when undertaken in the very early stages of the disease there is no cure by treatment, though spontaneous cure may occur. Thus, Impey in his Prize Essay writes that leprosy is not amenable to treatment, yet in certain cases the disease is cured. Though in others it may be temporarily arrested the disease as a rule goes steadily from bad to worse "till death removes the patient from a life that is almost worse than death." By 'spontaneous cure' Impey seems to have meant what we now call 'burned-out' cases. 'Self-cure' occurred only in anæsthetic leprosy. Study of several hundreds of cases at Robben Island, South Africa, showed him that the maximum duration of the disease was eleven years from the appearance of symptoms, if any live longer than that they enjoy good general health. Of 402 dying at Robben Island 292 died in two years and all but three within nine years of admission. Those living longer and enjoying fair health—Impey's 'self-cured' cases—die from some other disease.

We must also remember, when gauging the effects of any particular form of treatment, that care, good feeding and hygiene work much benefit without any specific, and improvement is often ascribed to some nostrum when these general measures have played the greater part.

The merest mention will suffice for some of the remedies which have been suggested from time to time in China, the home of leprosy, where naturally everything possible would be tried. As in England touching for King's Evil was for long thought to be efficacious, so we read of a case of leprosy being cured in the fourth century A.D. by the royal touch of the Emperor. Scorpions and snakes have always been credited with curative properties and snake medicine, *yu feng yao chiu*, is still made in Jukao and used for this disease. *Tsan Er* grass, the burdock, has been employed also for many years, perhaps for centuries. Again, tattooing of anæsthetic patches with Indian ink has been used and has its advocates.

In a work, *De Secretis Naturæ*, published in Amsterdam in 1790 and written in Latin, there is the statement "It ought to be known that the blood of dogs and of infants two years old and under, when diffused through a bath of heated water, dispels the leprosy without a doubt" (*absque dubio liberat lepram*).

But we must leave these and pass on to *Chaulmoogra*, the oldest remedy known and still the best.

Chaulmoogra was mentioned by Chu Tan Chi in the fourteenth century, but he did not speak very highly of its curative properties,

it is thought that the oil, being imported, was old and rancid before it was used. The Chinese have used it for centuries both internally and externally. Another favourite Chinese remedy is *Tai Fong Chee* and good results have followed its use. This is a powder and one of its chief ingredients is chaulmoogra. The preparation consists of the kernels of *Taraktogenus kurzii* (now *Hydnocarpus anthelmintica*) and the seeds of Pak chut lai (*Tributus terrestris*) and of Teh mah yan (*Cannabis indica*). In an old Chinese pharmacopœia *Tai fung chee* = great disease seeds. The plant is grown in India, Burma and Siam and is used as a parasiticide and in ulcers, ringworm and especially leprosy. The whole nut seems to give better results than the extracted oil. The two other constituents grow in China. Later, the second of these latter was omitted and the preparation contained three parts of the first to one of the second (seeds of *Tributus terrestris*).

Another remedy employed by the Chinese is *gurjun oil*, obtained from species of *Dipterocarpus*, it was given internally and also applied byunction in the form of a soapy emulsion with lime water.

All the noteworthy advances in the therapeutics of leprosy have been made in the past thirty or forty years, and among the earliest of these were vaccinal preparations. In 1906-07 Deycke employed his *Streptothrix leproides*, injecting it as a vaccine, and reported marked improvement in certain cases. He then proceeded to determine the active constituent of his preparation and concluded that it was, chemically, a neutral fat which he named *Nastin*. Injections of this ingredient caused intense reaction in the leprous tissues and the bacilli were observed to break up, lose their fatty coating and their acid-fast properties. For the more resistant cases he prepared a compound of this with 2 per cent benzoyl and called it *Benzoyl-nastin* or *Nastin B*. It was supposed that the benzoyl chloride removed the fat of the bacilli and the nastin then got to work on the organism itself. Deycke's favourable reports from its use were not confirmed, occasionally a case was said to have 'decidedly improved' but other writers expressed disappointment, some finding no improvement or very slight and that delayed, others reporting that it was quite inert except for local irritant effects. The preparation, however, continued to be used for some years.

The next vaccine preparation of any note was that of J. Hasson in 1926. He used a stock vaccine, injected weekly, consisting of 15,000 millions of *Ps pyocyanea* (then known as *Bacillus*

pyocyaneus) and 5000 millions of Hansen's bacilli in 2 c c of physiological saline. The latter organisms, since they could not be grown by ordinary methods of culture, were obtained from the serum of blisters produced over the site of a leprous lesion, the fluid was kept in an incubator at 36° C for 50-60 days Hasson in his article reproduces photographs of three patients showing the improvement after treatment, but two of them had also received chaulmoogra or hydnocarpate, and the other had had a preparation known as *éparséno*

Yet another vaccine calling for notice is that of Vaudremer who in 1935 cultivated sterile fragments of leprous nodules on an aspergillus medium (see above) and he then subcultivated what he regarded as evolutionary forms on gelatin and, for use as a vaccine, sterilized this with iodine He injected subcutaneously and twice weekly the bacilli lysed in saline, starting with 0.25 c c and increasing gradually to 2 c c, which was never exceeded, and with the higher doses the interval was lengthened to a week It did not prove very satisfactory and the most favourable reports were that it lessened pigmentation and infiltration, but had no effect on the leprous nodules, moreover, it was harmful in patients with ocular complications

About the time when Deycke was bringing forward his nastin, Rost was using *leprolin*, a preparation analogous with tuberculin, both diagnostically and therapeutically, but it never had much vogue

We now pass on to *Chaulmoogra*, the only drug which has maintained its place after centuries of trial and that itself even has narrow limitations It will cure only after a prolonged course and then not unless the patient starts the treatment in an early stage and persists with it We have mentioned chaulmoogra itself and the oil prepared from it, in the last twenty years preparations made from it rather than the whole product have been more widely used

In 1916 Sir Leonard Rogers reported beneficial effects from the use of chaulmoogra fatty acids, and the following year announced that he obtained better results with sodium salts of the fatty acids of higher than with those of lower melting-point In that and the next year he recorded more beneficial results from the use of sodium gynocardate together with sodium morrhuate, prepared in the same way and his results were confirmed by Peacock in Mandalay, Carthew in Siam and Muir in Orissa Horder of Pakhoi, twenty years before, had said that he found it best to

put his patients under good hygienic conditions and treat them as he would cases of chronic phthisis, that is, with *Oleum morrhue*

Rogers's method was to administer 0.5 c.c. sodium gynocardate intravenously on the first day, half this together with 0.25 c.c. sodium morrhuate by the same route on the third day, and 0.5 c.c. of the morrhuate intramuscularly on the fifth day. During the succeeding weeks the dose is increased by increments of 0.5 c.c. to a maximum of 5 c.c., so long as there is no febrile reaction. If there is a rise of temperature, the dosage is at once halved and then gradually raised again up to 1 c.c. less than the former fever-producing dose. The injections are continued for some months after the symptoms disappear. Though this was reported on as continuing to give good results, Rogers the following year suggested the use of sodium soyate (from Soya bean oil, *Soja hispida*) as less irritating, but this was found not to be so good. In 1922 what is known as E.C.C.O. mixture was introduced by E. Muir. This is named from the initial letters of the four ingredients, it is composed of ethyl esters of the fatty acids of *Hydnocarpus wrightiana* oil, 1 c.c., pure (doubly distilled) creosote, 1 c.c. (as antiseptic), camphor 1 gm., and olive oil 2.5 c.c. It is given twice a week intramuscularly, the initial dose being 0.25 c.c. and increasing by this amount to a maximum of 5 c.c. In 1919 H. T. Holman and A. C. Dean recommended the use of ethyl esters of the chaulmoogra fatty acids.

Bayer's 'antileprol' is an ethyl ester preparation of chaulmoogra, it was said to be better tolerated than the oil itself, to have an action equal to that of the oil and not to produce the by-effects of the latter.

The British Empire Leprosy Relief Association founded in 1924 and its policy in promulgating information concerning the disease and supplying drugs have already been referred to.

During the next nine or ten years various drugs were brought upon the market, but all prepared from, or based on, chaulmoogra, such as injection of iodized esters of its active components, used in the Philippines, alepol (introduced by Burroughs, Wellcome) or sodium hydnocarpate, the sodium salts of a fraction of the fatty acids of lower melting-point, used in Africa in 1928, Muir's creosoted hydnocarpus oil in India. Changes also took place in the mode of administration, as by injecting the ethyl esters in drop doses at numerous points in affected areas of the skin, the lesions were said to clear up more rapidly under such treatment (see below, Plancha method).

In 1929 L. Stévenel carried out experiments to determine the

active principle of chaulmoogra oil He found that oil from seeds carefully decorticated was non-toxic, as were also albuminous extracts from the residue In fact, only the integument was found to contain the toxin, and thus was present in an ethereal extract of the powdered integument Further, he found that the toxic ethereal extract is the active moiety This extract consists of non-saponifiable substance to the extent of about 5 per cent, the remaining saponifiable material is non-toxic and therapeutically inactive The active principle could be obtained in crystals, resembling, and perhaps actually, a form of phytosterine, vitasterine or lipoid, present exclusively in the hard integument of the seeds In a summary Stévenel writes The active principle of chaulmoogra oil, readily soluble in fats, comes exclusively from the integument "From the practical point of view, therefore, the oil should be extracted by treating with olive oil the entire seed with the integument, but freed from the fruit-pulp which contains a cyanogenetic glucoside"

The Plancha or 'infiltration' method mentioned above consists of injections into the skin affected with the object of producing a weal not more than 1 cm in diameter, and the total amount injected must not exceed double the usual intramuscular dose, 4-5 c c, of the ethyl esters Macules were found to respond best, nodules least, and the combined intramuscular and local injections proved more effective in obtaining a bacteriologically negative condition than the former alone The local destruction of the bacilli and the increased lipase produced are believed to play a part in bringing about this result

About the same time, 1928-9, the ethyl esters of *Calophyllum bigator*, the Dido tree of Fiji, the tamanu of Tahiti, were being tried The oil obtained in the native way proved better than that extracted *secundum artem* The greenish-white kernel is cut up or crushed, and spread on sheets of corrugated iron placed in a sloping position in the sunlight In two or three days the oil trickles out and is caught below, the remnants of the oil are obtained by means of a hand-press Twelve bushels of nuts yield only two quarts of oil and the product is usually mixed with coco-nut oil It had been used for years in Fiji as an embrocation and also for general application The superintendent at Makongai leper settlement used it at first as an embrocation for leprosy neuralgia and then began to inject it in doses of 0.5-0.6 c c intramuscularly once a week Later he employed from four to even ten times this amount, and found it excellent for the neuritis and general pains, but not so efficacious as the chaulmoogra in the disease itself

We cannot speak in detail of the many suggested methods of treatment such as by gold salts—solganal, sanocrysin, allochrysin, krysolgan and others—employed on the analogy of benefits obtained in some cases of tuberculosis, of solid carbon dioxide and trichloroacetic acid locally, zinc ionization for trophic ulcers, tellurium, calcium chloride, endocrines, thyroid, pancreas, pituitrin, radium and X-rays, snake-venom, bee-stings, and most recently, methylene-blue. All came into use, or perhaps we should say were given a trial in the last ten or twelve years, some reported well, usually in a few cases only, others found them ineffectual. Two, however, call for a few words, namely potassium iodide, and protein shock, and for the leprous reaction ephedrine.

The use of potassium iodide was not new, it was indeed an old remedy, but fell into disrepute because of the severe reactions it occasionally set up. Cochrane put its use on a more rational basis in 1928. He pointed out that if the breaking down of leprosy foci causes fever which leaves the patient ill and incapacitated it is harmful, but in stronger subjects able to take adequate exercise the breaking down of a few foci may, by setting free bacilli, stimulate the defences. Thus, it is useful in early skin cases, dangerous in the advanced nodular cases with vast numbers of bacilli. Similarly, some strong early nerve cases benefit, but many do not. Hence the iodide should be given only to those in fairly robust general health, apart from the leprosy, and not be kept up too long even in them, since repeated reactions are harmful. Cochrane is of opinion also that in those apparently cured it is better not to risk a flare up by giving large doses of iodide. Canaan tried it in Palestine and concluded in 1929, after a nine-months' trial, that it is not free from danger, very few of his patients tolerated it well, some reacted quickly and favourably but it was not possible to foretell who would and who would not.

Isabel Kerr, at the Victoria Leper Hospital, Dichpali, made some useful observations on the use of iodide as directed by the results of the corpuscle sedimentation test. She found that a low sedimentation rate, under 30, indicated good resistance, and under such circumstances the iodide could be used safely with hydriocarpates, if 40 or more, resistance was low and iodides, even in small doses, were harmful, and no iodide should be given as long as the slightest reaction is produced by hydriocarpate injections.

Protein shock, in 1929–30, enjoyed some degree of popularity in the treatment of several conditions, leprosy among them. In

some cases milk was used, in others a heterologous vaccine, as *Bact typhosum* or TAB. At Kisumu, Kenya Colony, the former was tried. Four c.c. of condensed milk were emulsified in 12 c.c. sterile distilled water to which was added 1 grain of antimony tartrate. This was administered intravenously, a sharp reaction followed, passing off in half an hour or so, except for a rise of temperature some six hours later. It was observed that the skin became whitish and scaly, desquamation took place, nodules tended to shrivel and ulcers healed. In Nigeria, at the Calabar Hospital, *Bact typhosum* vaccine was used, 500,000 organisms being injected intravenously every five days or so according to the results obtained. After eight injections the reactions were so slight that inoculations were discontinued. Nine patients were treated in this way and all said that they felt better and had less pain, but we must remember that the psychological effect of acupuncture in the native is at times remarkable and interpretation of subjective accounts must be guarded. Three showed some improvement, six none, objectively.

Ephedrine was used as a substitute for adrenalin in the treatment of the leprosy reaction in 1928-9. Muir and Chatterji describe its mode of action in relieving the pains of leprosy. Not only are the effects greater but they are more lasting than those with adrenalin and there is the additional advantage of acting when taken by mouth. The organism of leprosy when localized in the nerve-trunks causes proliferation of the neuroglia and this continues even during the quiescent phases of the disease, when reaction occurs there is engorgement of the granulation tissue and increased pressure on the nerve. Ephedrine, by contracting the arterioles, reduces the engorgement and gives relief.

In 1929 Sir Leonard Rogers, in his Cameron Prize Lecture, delivered at Edinburgh, summed up the recent advances in treatment and sounded a useful and, indeed, much needed note of warning to those who are inclined to publish unduly optimistic reports on some new alleged remedy after only a short period of trial and observation of a small series of cases.

The gauging of results of any particular form of treatment of leprosy is a difficult matter, because in the first place improvement occurs when patients are put under circumstances of good hygiene apart from any specific treatment, and, secondly, the disease may exhibit spontaneous remissions.

Apart from mineral substances—mercury, arsenic, antimony, potassium iodide, iodoform—and organic substances—guaiacol,

thymol, ichthyol—and organic products—thyroid, pituitrin, adrenalin, and local measures such as caustics, excision, the use of carbon dioxide snow, radium, trichloroacetic acid and so on, the treatment may be summed up as follows. Some forty years ago serum was tried extensively and, as already mentioned with most new drugs and methods, good reports were issued, but its reputation was not sustained, specific vaccines (so-called, because the preparations contained lepra bacilli, but not cultures comparable with other vaccines) have been in use for nearly a quarter of a century, and again at first reports were favourable, but no lasting cures were recorded. Under this head would also come tuberculin, tried in 1892 for leprosy. This was found occasionally to bring slight transient amelioration. Nastin, prepared from Deycke's *Streptothrix*, and Nastin B, the same with addition of benzoyl chloride, were introduced in 1909, and Rost's leprolin and lepra nodules containing bacilli in 1910, and Hasson's method of the fluid of blisters over lepromata. Injection of other vaccines made of acid-fast and non-acid-fast bacilli might produce reactions and subsequent improvement, but not permanent benefit, they probably acted by protein shock.

The only drug which has stood the test of time is chaulmoogra and its constituent acids, chaulmoogric, hydnocarpic and gyno-cardic, the last a mixture of fatty acids of low melting-point. *Taraktogenus kurzu* is the source of chaulmoogra oil and the chief constituent of the Chinese remedy Tai Fong Chee, *Hydnocarpus wightiana* and *H. anthelmintica* are the sources of hydnocarpus oil. Chaulmoogra was at first given orally with good results in early cases. In 1894 injections, subcutaneous and intramuscular, were given in Egypt by Tourtoulis, and combined with oral administration by Hallopeau in France. Heiser in 1913 used what was known as Mercado's formula, or chaulmoogra injections with camphorated oil, to ease pain, and resorcin as an antiseptic. Two years later, in 1915, advance was made when Rogers started the use of the sodium salts of the acids in solution, interjecting them in 3 per cent solution, at first subcutaneously, later intramuscularly and finally intravenously. As stated above, he found the salts of the higher melting-points more effective than those of the lower. By intravenous administration pain is avoided, but the vein soon becomes blocked by inflammatory products. In 1918 Rogers and Ghosh used the esters of chaulmoogra oil, but these caused much pain. Other oils now were tried, namely, those of *Nieha azadirachta* (mim oil) and cod-liver oil, linseed oil and soya bean (as already mentioned).

The esters of chaulmoogra were given subcutaneously, intramuscularly, or infiltrated into points of lesions. After a certain, or rather uncertain, period sensitization resulted, evidenced by the leprous reaction and the treatment had to be suspended or modified in the first or second stages, at least if these reactions were frequent. In the third stage it might be followed by resolution of lesions and so benefit. The beneficial effects of chaulmoogra, and of the other oils (such as Dilo oil in Fiji), when such occurred, were due in part to the reactions produced—to a certain extent the greater the irritation the greater the beneficial results.

Many doubt whether actual cure is possible. The 'burned-out' late stages, though no longer infective, cannot be regarded as cures, though the term 'absolute cure' is used for those who have reached this stage. In the earlier stages arrest is possible, but to obtain it the patient must be, apart from the leprosy, in good general health, removed from insanitary and debilitating influences, and be able to tolerate prolonged treatment and fairly large doses. A patient is regarded as 'relatively cured' if he shows no active signs for two years after cessation of treatment and if he is bacterially negative. We must remember that the bacilli may lie latent for long periods, perhaps for years, and then assume pathogenicity and start fresh lesions, and, on the other hand, general treatment, apart from specific, and removal of concomitant disease—syphilis, ankylostomiasis, dysentery—are essential if amelioration is to be attained, and removal of these, aided by improvement of general hygienic surroundings and mode of life, may of themselves be followed by benefit to the leprotic state before any specific treatment is adopted. Hence the difficulty of gauging how much of the betterment is due to specific treatment and how much to improved conditions of living, and hence also the danger of undue extolling of new remedies when they are accompanied by these environmental improvements.

The question of treatment as it stands to-day, as summed up by Rogers and Muir, probably our greatest authorities on the subject, may be stated as follows. It is useless to attempt cure if the patient is not under the best general conditions—in healthy, sanitary surroundings, with regular, proper diet, and removed from all sources of worry, relieved of anxiety regarding his family. Specific treatment should be started as early as possible and continued long after objective signs have disappeared. An analysis of over 4000 cases treated at the Culion Settlement in the Philippines showed that after three months' continued treatment with chaulmoogra or the hydnocarpate derivatives 25 per cent

had improved, after six months 46 per cent, after nine months 74 per cent, after a year 81 per cent, and after fifteen months 93 per cent. Cases of only one to two years' duration improved most, those of longer duration progressively less

The improved methods of dealing with leprosy [they state] have therefore placed in our hands a simple and effective means of diminishing the disease by providing treatment, under attractive conditions, for early little- or non-infective cases in out-patient dispensaries and more advanced infective types in sanatoria and colonies, only funds and organization being required to bring about a great decrease of the disease in all countries where these advantages can be supplied to a large proportion of the lepers, and that, too, with a minimum of suffering, physical and mental, attendant on the segregation methods on which we have hitherto been almost entirely dependent

In conclusion, it may be of interest to note a few important dates in the history of leprosy, more particularly as regards Great Britain, to the discovery of the bacillus

- B C
 60 Leprosy thought to have been first brought to England
 53 Celsus wrote on the disease
- A D
 432 First notice of leprosy in Ireland
 500 Charaka wrote on leprosy
 549 Council of Orleans Leprosy decree
 550 Outbreak (pestilence) of leprosy in Ireland
 583 Council of Lyons Leprosy decree
 869 Leper houses in Ireland (earlier, in the seventh century, on the Continent and much earlier in Palestine)
 940 Leprosy prevalent in England, at various times during the tenth century on the Continent
 958 Leprosy mortality excessive in Europe
 959 Leprosy recognized as a valid cause for divorce
 1080 Several leper-houses in England (before the First Crusade)
 Twelfth century Persecution and burning of lepers Several decrees
 Seventeenth century Lepers much fewer, in England at least
 1676 Fernellus and Toustus question the contagiousness of leprosy
 1730 Leprosy prevalent in Ireland
 1753 Leprosy prevalent in St Kilda
 1775 Last endemic case in Ireland, at Waterford (?)
 1809-10 Isolated cases in Great Britain
 1867 Report of the Royal College of Physicians.
 1874 Hansen's discovery of the bacillus

